

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro



(43) Internationales Veröffentlichungsdatum
7. April 2005 (07.04.2005)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2005/030332 A2

(51) Internationale Patentklassifikation⁷: **A61P 25/28**,
25/14, 25/16, 3/10, 25/08, 9/10, 25/00, A61K 31/55, C07D
491/10

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(21) Internationales Aktenzeichen: PCT/AT2004/000251

(22) Internationales Anmeldedatum:
12. Juli 2004 (12.07.2004)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(81) Bestimmungsstaaten (soweit nicht anders angegeben, für
jede verfügbare nationale Schutzrechtsart): AE, AG, AL,
AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(30) Angaben zur Priorität:
A 1538/2003 29. September 2003 (29.09.2003) AT

(84) Bestimmungsstaaten (soweit nicht anders angegeben, für
jede verfügbare regionale Schutzrechtsart): ARIPO (BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Veröffentlicht:

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kürzungen wird auf die Erklärungen ("Guidance Notes on Co-
des and Abbreviations") am Anfang jeder regulären Ausgabe der
PCT-Gazette verwiesen.

(54) Title: USE OF GALANTHAMINE AND THE DERIVATIVES THEREOF IN THE PRODUCTION OF MEDICAMENTS

(54) Bezeichnung: VERWENDUNG VON GALANTHAMIN UND SEINEN DERIVATEN ZUM HERSTELLEN VON ARZNEI-
MITTELN

(57) Abstract: The invention relates to the use of galanthamine and the cholinergically active derivatives thereof in the produc-
tion of medicaments for preventive treatment of postoperative delirium and/or subsyndromal postoperative delirium. Galanthamine,
the galanthamine derivative (4aS, 6R, 8aS)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef] [2]ben-
zazepinium bromide and analogous salts, hydrates or solvates are advantageously suited for use according to the invention.

(57) Zusammenfassung: Die Erfindung betrifft die Verwendung von Galanthamin und seinen cholinerge Aktivität aufweisenden
Derivaten zum Herstellen von Arzneimitteln zur Behandlung sowie zur präventiven Behandlung von postoperativem Delir und/oder
subsyndromalem postoperativem Delir. Neben Galanthamin eignet sich in vorteilhafter Weise das Galanthaminderivat (4aS, 6R, 8aS)-
6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef] [2]benzazepinium Bromid sowie analoge Salze,
Hydrate oder Solvate für die erfindungsgemäße Verwendung.



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Verwendung von Galanthamin und seinen Derivaten zum Herstellen von Arzneimitteln

Die Erfindung betrifft die Verwendung von Galanthamin und seinen Derivaten zum Herstellen von Arzneimitteln zur Behandlung des postoperativen Delirs.

Trotz deutlicher Fortschritte in der Anästhesie sowie in der perioperativen Versorgung kommt es auch heute bei einem erheblichen Anteil der Patienten, an denen größere chirurgische Eingriffe vorgenommen werden, zu postoperativen psychiatrischen Komplikationen, die unter dem Sammelbegriff „postoperatives Delir“ bekannt sind.

Als Delir bezeichnet man einen Zustand gestörten Bewusstseins, charakterisiert durch allgemeine Verwirrung, Herabsetzung der kognitiven Funktionen (Aufmerksamkeit, Konzentration und Gedächtnis), Halluzinationen und labiler Emotionen. Damit weist das Delir Elemente der Demenz wie auch psychotischer Zustandbilder auf, ist aber von diesen vor allem durch seine akute Natur und die meist spontan eintretende, wenn auch oft unvollständige und verzögerte, Reversibilität abgegrenzt.

Im Gegensatz zu den degenerativen Demenzsyndromen liegt beim postoperativen Delir eine ausschließlich funktionale Störung des zentralen Nervensystems vor. Das durch die einzelnen psychiatrischen Symptome erzeugte klinische Bild kann sehr schnell - gelegentlich innerhalb von Sekunden - fluktuieren.

Ein akutes oder subakutes Delir (entsprechend den Klassifikationen ICD 293.0 bzw. 293.1 der Weltgesundheitsorganisation) ist oft durch Einnahme von pharmakologisch wirksamen Substanzen induziert. Zahlreiche solche Substanzen sind Wirkstoffe oder Metaboliten von Medikamenten, sodass ein arzneimittelinduziertes Delir (ICD 292.81) gegeben ist. Insbesondere Medikamente mit anticholinergischer Wirkung, die das auf dem Neurotransmitter Azetylcholin basierende Nervensystem teilweise blockieren, können ein Delir induzieren, jedoch auch Sedativa, wie Benzodiazepine, und Antimanika wie Lithiumsalze.

Auch Rauschmittel bzw. deren akuter Entzug nach chronischem Gebrauch können Delirien erzeugen. Sehr häufig ist dies bei massivem akutem Alkoholabusus bzw. im Alkoholentzug der Fall (ICD 291.0), jedoch können auch Cannabisprodukte, Amphetamine, Kokain usw. delirante Zustände verursachen.

Während die genannten deliranten Bewusstseinsveränderungen eine neurochemisch direkt nachvollziehbare Ursache haben, gibt es auch Delirien letztlich unbekannter Genese, worunter trotz des bekannten Auslösers (chirurgischer Eingriff) auch das postoperative Delir zu rechnen ist, da kein zugrunde liegender pathologischer Mechanismus zweifelsfrei bekannt ist.

Das postoperative Delir (POD) wird heute als ein multifunktionelles Syndrom angesehen ⁽¹⁾; wobei das Alter und der allgemeine Gesundheitszustand des Patienten ebenso eine Rolle spielen wie eventuell präoperativ vorhandene kognitive Störungen, nicht näher definierte Einflüsse der verabreichten Narkosemittel, und möglicherweise auch bestimmte intraoperative physiologische Veränderungen ⁽²⁾. Obwohl ein POD durchaus unmittelbar nach dem Erwachen aus der Narkose vorhanden sein kann, ist es nicht mit der schnell vorüber gehenden gutartigen Desorientierung nach Anästhesie gleichzusetzen. Vielmehr kann ein POD durchaus auch erst am zweiten postoperativen Tag oder auch noch später einsetzen, nachdem das eigentliche Erwachen aus der Narkose klinisch unauffällig verlaufen ist. Somit ist in diesen Fällen eine direkte Wirkung der perioperativ verabreichten Anästhetika bzw. Analgetika auszuschließen.

Obwohl die wissenschaftliche Literatur widersprüchliche Angaben über die Inzidenz des POD enthält (was größtenteils auf Unterschiede in den untersuchten Patientenpopulationen und die verwendete psychiatrische Definition zurückzuführen ist), besteht doch allgemeine Einigkeit, dass es sich um ein durchaus häufig auftretendes Phänomen handelt ⁽³⁾, insbesondere nach großen orthopädischen Eingriffen ⁽⁴⁾ und vor allem bei älteren Patienten. Eine jüngst publizierte Studie ⁽⁵⁾ fand unter Verwendung der als klinisch sehr relevant geltenden Confusion Assessment Method (CAM; ⁶⁾ unter 2158 postoperativen Patienten 16% mit voll ausgeprägtem Delir, 13% mit mindestens zwei Schlüsselsymptomen, und 40% mit mindestens einem Symptom, während nur 32% symptomfrei waren.

Obwohl POD also häufig und fast ausschließlich bei stationär aufgenommenen Patienten auftritt, und obwohl es als schlechtes prognostisches Zeichen für den weiteren postoperativen Verlauf gilt, wird dieser Zustand häufig nicht bemerkt oder nicht beachtet. Dies ist vor allem darauf zurückzuführen, dass postoperative Patienten in der Regel auf den zuständigen chirurgischen Abteilungen verbleiben und das dortige Personal

apathiebetonte (hypoaktive) Delirien oft nicht erkennt. Nur verhaltensauffällige (hyperaktive) Patienten werden mit Antipsychotika und/oder Sedative therapiert ⁽⁷⁾. Dabei wäre bereits die Therapie des sogenannten subsyndromalen POD (das nicht alle geforderten psychometrischen Kriterien eines POD erfüllt) äußerst bedeutsam, da dessen Bestehen einen Risikofaktor für die Progression zum Vollbild des deliranten Zustandsbildes darstellt, was statistisch gesehen mit verlängertem Spitalsaufenthalt, erhöhter Mortalität nach Entlassung, und verminderter kognitiver Leistung bei späteren Kontrolluntersuchungen einhergeht ⁽⁸⁾; bei den letztgenannten Spätfolgen spricht man auch vom Zustandbild des Postoperative Cognitive Decline (POCD), das in die Demenz übergehen kann.

Die Verwendung von Cholinesterase-Inhibitoren zur Therapie von arzneimittelinduzierten Delirien ist seit geraumer Zeit bekannt. Dies gilt vor allem für das „zentrale anticholinerge Syndrom“ ⁽⁹⁾, jedoch auch für Delirien, die im unmittelbaren Anschluss an Behandlungen mit nicht unmittelbar anticholinerg wirkenden Arzneimitteln auftreten. Beispielhaft erwähnt sei die Anwendung des prototypischen Cholinesterase-Inhibitors Physostigmin bei diesbezüglichen Komplikationen mit nicht-narkotisch wirkenden Akut-Sedativa ⁽¹⁰⁾.

Die dabei gemachten vorteilhaften Erfahrungen wurden auch auf das POD übertragen. Bereits 1978 wurde in der Literatur zur Vermeidung deliranter Zustände nach der Beendigung der Narkose die Injektion einer Einzeldosis Physostigmin unter noch aufrechter Narkose empfohlen ⁽¹¹⁾. Die Therapie eines bestehenden, insbesondere eines sich erst nach einer luziden postoperativen Periode manifestierenden, Delirs wird jedoch nicht angesprochen, sodass diese Anwendung als intraoperative Prophylaxe eines substanzinduzierten (nämlich unmittelbar mit den Effekten des Narkosemittels in Zusammenhang stehenden) Delirs gewertet werden muss.

Die WO 00/032185 A offenbart Effektoren des cholinergen Systems zur Therapie von Delirien, darunter auch des PODs, das als „nicht cholinerges Delir“ bezeichnet wird. Darunter wird in der WO 00/032185 A ein Delir verstanden, das entsteht, ohne dass innerhalb der vorhergehenden 48 bis 72 Stunden eine Behandlung oder Intoxikation mit Substanzen erfolgt ist, die das cholinerge Reizleitungssystem blockieren. Die in der WO 00/032185 A

geoffenbarte Anwendung von Cholinesterase-Inhibitoren zum Behandeln des PODs soll nach einer Operation erfolgen. Konkrete Beispiele für die Verwendung von Galanthamin und seinen Derivaten zum Behandeln von PODs enthält die WO 00/32185 A nicht. Die WO 00/32185 A enthält als einziges Beispiel den Fall einer Patientin, die im Zuge der medikamentösen Therapie ihrer langjährig bestehenden bipolaren Störung eine Lithium-Intoxikation erlitten hatte und deren daraufhin eintretendes Delir mit dem Cholinesterase-Inhibitor „Rivastigmin“, einen irreversiblen Inhibitor der Cholinesterasen, der seine Wirkung durch kovalente Modifikation (Carbamylierung) dieser Enzyme ausübt, erfolgreich therapiert wurde. Dabei handelt es sich um ein arzneimittelinduziertes Delir.

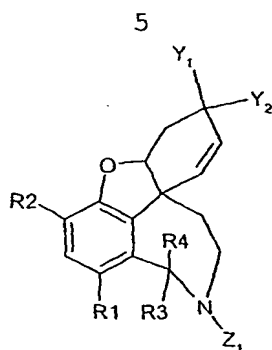
Derzeit gibt es kein für die Indikation POD zugelassenes Arzneimittel sowie keine veröffentlichten systematischen klinischen Studien, die die spezifische Wirksamkeit eines Arzneimittels bei streng definiertem POD wissenschaftlich unterstützen. Somit besteht nach wie vor ein erheblicher medizinischer Bedarf an pharmakologischen Mitteln, die ein auftretendes POD schnell beenden. Dabei muss auf minimale Nebenwirkungen einer solchen Therapie besonderer Wert gelegt werden, da sich ein POD-Patient per definitionem in der postoperativen Erholungsphase befindet und daher eine reduzierte physiologische und psychologische Stresstoleranz aufweist.

Der Erfindung liegt die Aufgabe zugrunde, diesem Bedarf gerecht zu werden.

Erfindungsgemäß wird die Verwendung von Galanthamin und seinen cholinerge Aktivität aufweisenden Derivaten zum Herstellen von Arzneimitteln zur Behandlung von postoperativem Delir und/oder subsyndronalem postoperativem Delir vorgeschlagen.

Weiters wird erfindungsgemäß die Verwendung von Galanthamin und seinen cholinerge Aktivität aufweisenden Derivaten zum Herstellen von Arzneimitteln zur präventiven Behandlung von postoperativem Delir und/oder subsyndronalem postoperativem Delir vorgeschlagen.

Vorzugsweise werden Galanthaminderivate mit der allgemeinen Formel Ia



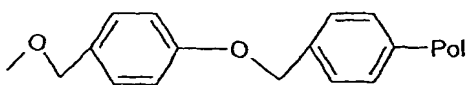
Ia

oder deren Salze verwendet, worin

- R_1 gleich H, verzweigtes oder geradkettiges (C_1-C_6) alkyl, Br, NO_2 , NR_5R_6 ist,
- R_5 und R_6 gleich oder verschieden sind und H, verzweigtes oder geradkettiges (C_1-C_6) alkyl bedeuten,

und worin

- R_2 gleich OH, verzweigtes oder geradkettiges (C_1-C_6) alkyl, methoxy, phenyloxy ist oder folgende Gruppe



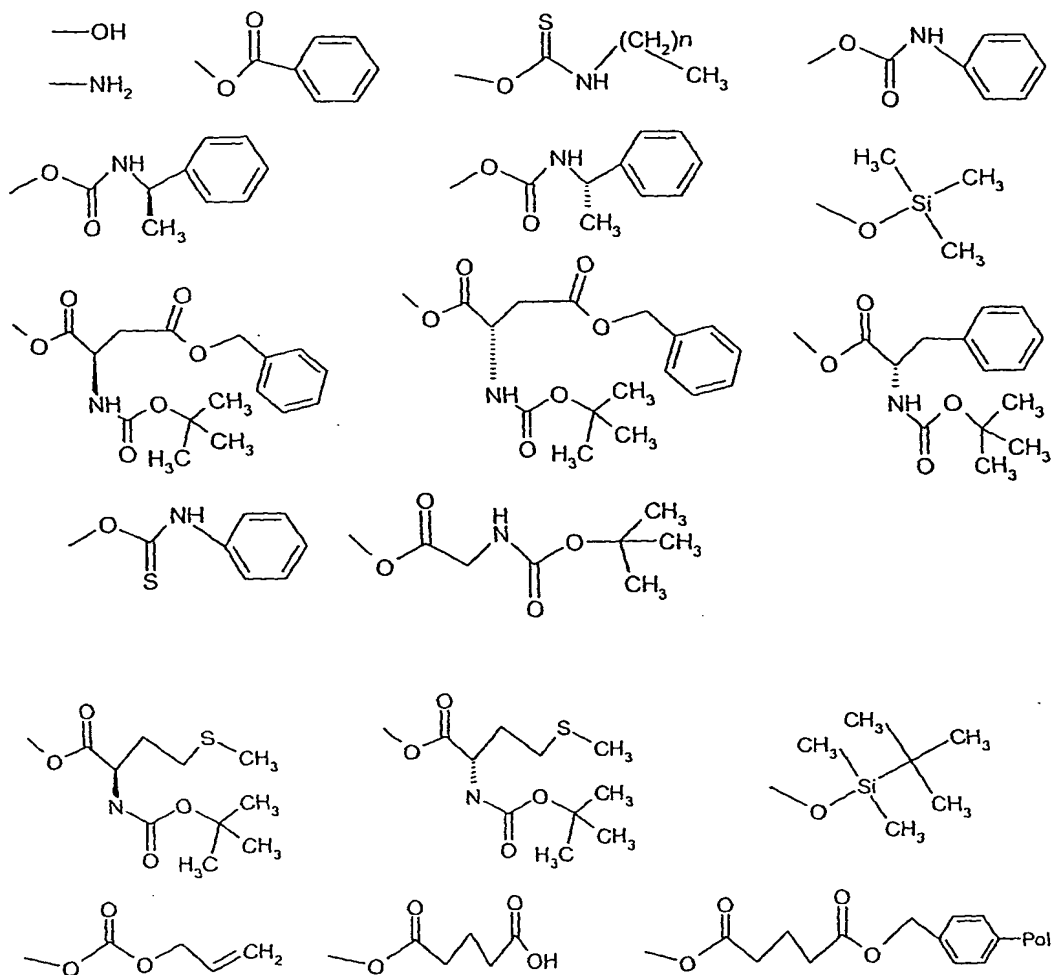
bedeutet, wobei Pol ein Polymer, vorzugsweise eines gemäß WO-A1-01/174820 ist, und worin

- R_3 und R_4 entweder gleichzeitig oder wechselweise H, D, CN, geradkettiges oder verzweigtes (C_1-C_6) alkyl oder gemeinsam eine Carbonylgruppe bedeuten,

worin weiters

- Y_1 und Y_2 wechselweise H oder eine Gruppe ausgewählt aus:

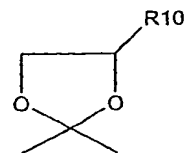
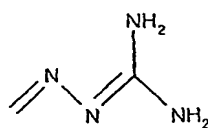
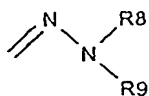
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sind, wobei n einen Wert von 0, 1 bis 15 darstellt, und Pol die oben angegebene Bedeutung hat, und wobei weiters

o Y_1 und Y_2 gemeinsam eine Carbonylgruppe ($=O$), $=NH$, $=N-$ OR₇, darstellen, wobei R₇ gleich H, Tosyl oder verzweigtes oder geradkettiges (C₁-C₆) alkyl ist,

o oder Y_1 und Y_2 gemeinsam eine Gruppe ausgewählt aus :

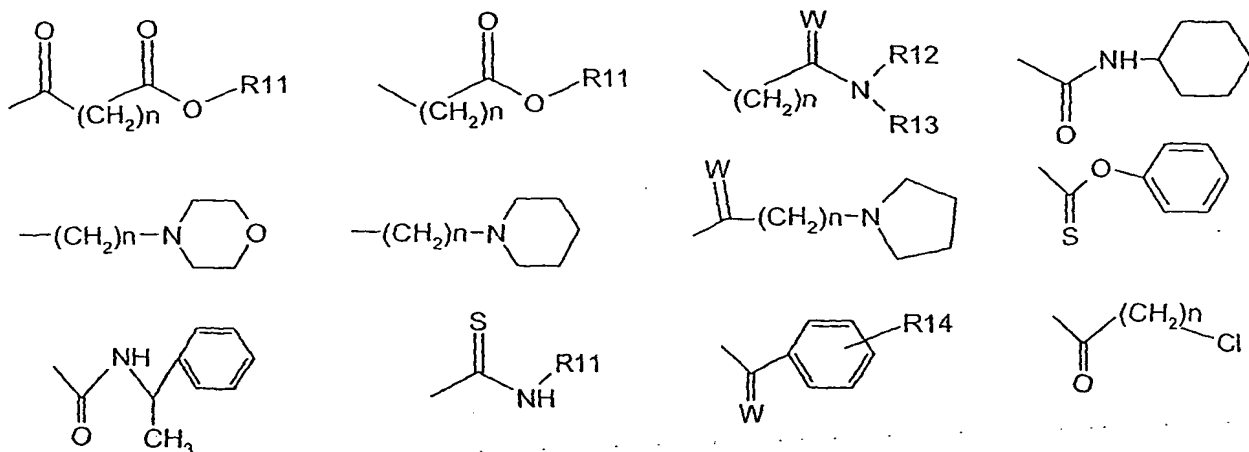


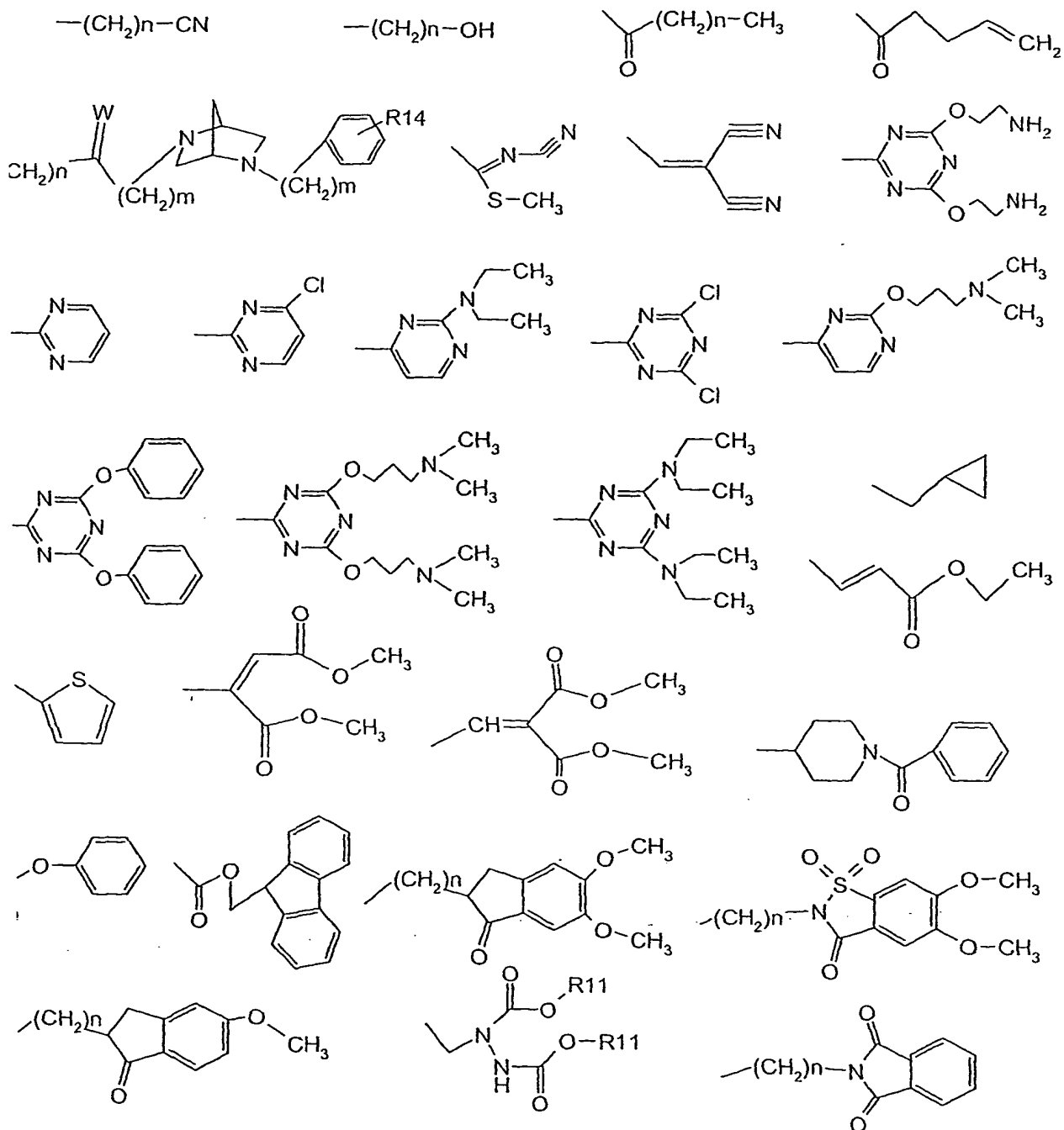
bilden, wobei R_8 und R_9 gleich oder verschieden sind und H, verzweigtes oder geradkettiges (C_1 - C_6) alkyl, $-(CH_2)_2-OH$, CHO, $CONH_2$, tBOC (terc. Butoxycarbonyl), oder $-COCOOH$ bedeuten, R_{10} gleich H oder CH_3 ist, und wobei für Y_1 gleich $-O-(CH_2)_2-OH$ Y_2 gleich OH ist,

und worin

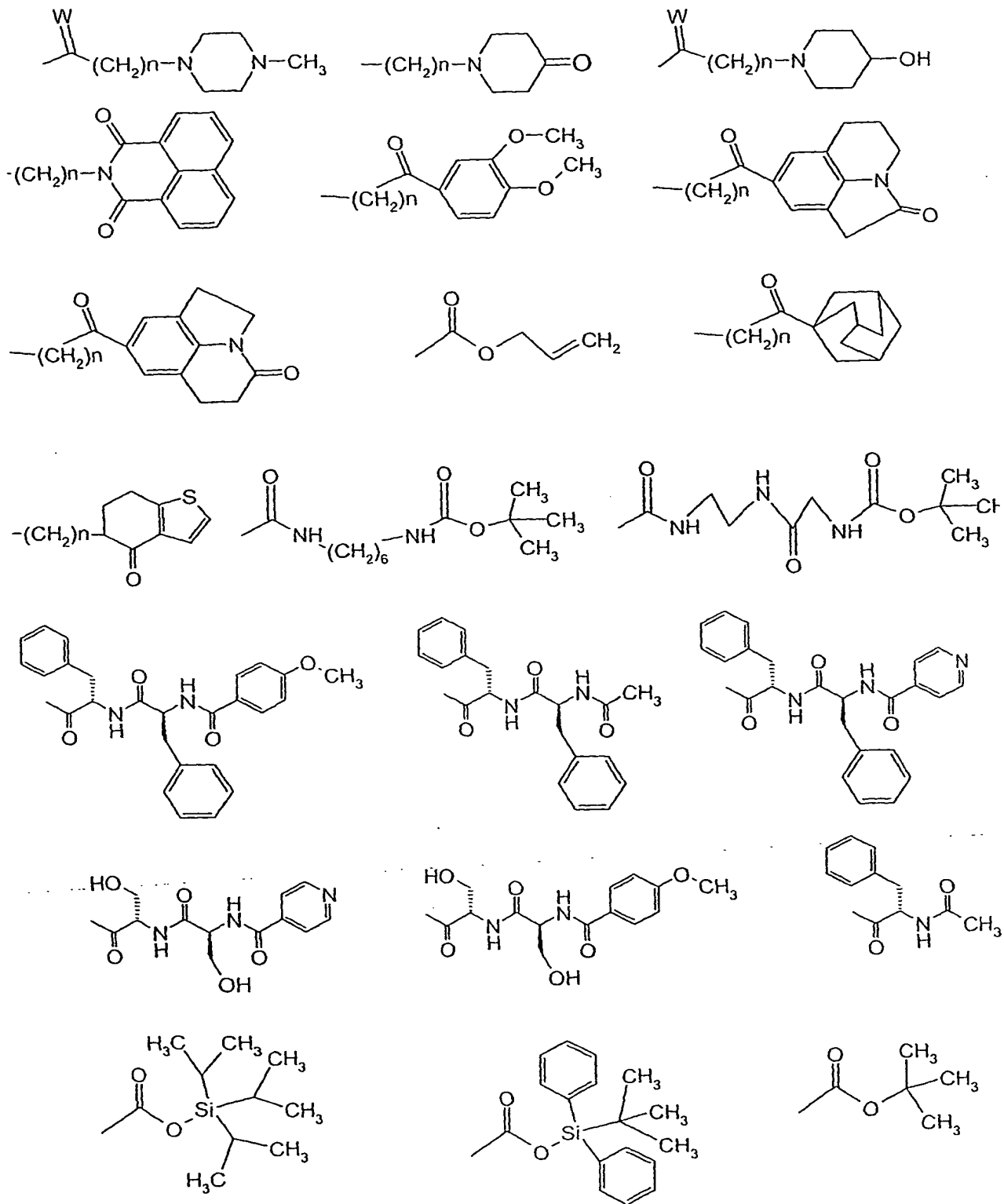
- Z_1 gleich H, verzweigte oder geradkettiges (C_1 - C_6) alkyl, (C_2 - C_7) alkenyl (C_2 - C_7) alkynyl, trifluoracetyl, formyl, phenyl

oder eine Gruppe ausgewählt aus:





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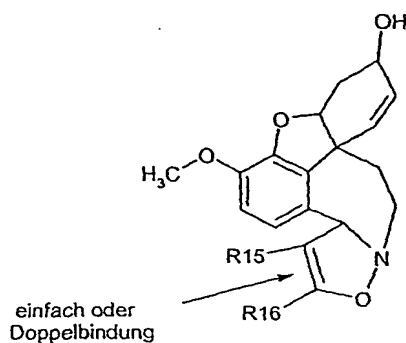
bedeutet, wobei R_{11} gleich H, geradkettiges (C_1 - C_6) alkyl, verzweigtes (C_1 - C_6) alkyl oder (C_2 - C_7) alkenyl ist, R_{12} und R_{13} gleich oder verschieden sind und H, geradkettiges oder verzweigtes

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(C₁-C₆) alkyl, phenyl, chlorphenyl, (trifluormethyl)-phenyl oder 1-naphtyl bedeuten, wobei R₁₄ gleich H, F, CH₃, NO₂, Cl, Br, J, CF₃ ist, n die oben angegebene Bedeutung hat, m gleich 0 oder 1 ist, und W die Bedeutung H oder O hat,

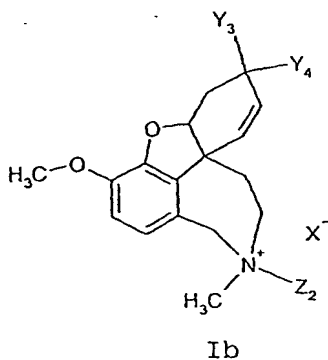
und worin weiters

- Z₁ und R₃ einen gemeinsamen Ring



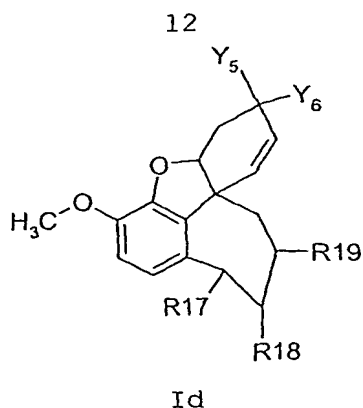
bilden, wobei R₁₅ und R₁₆ wechselweise H, COOCH₃, COOCH₂CH₃, CN, COCH₃ bedeuten.

Vorteilhafterweise werden auch Galanthaminderivate mit der allgemeinen Formel Ib



verwendet, worin

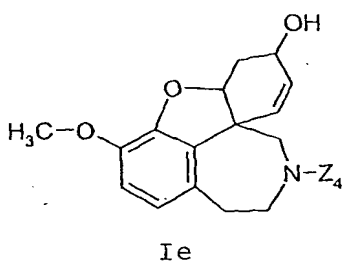
- Y₃ und Y₄ wechselweise H und OH bedeuten,
- X gleich Cl, Br oder I ist,



oder deren Salze, worin

- Y_5 und Y_6 wechselweise H oder OH bedeuten oder gemeinsam eine Ketogruppe bilden, und
- R_{17} , R_{18} , R_{19} wechselweise für je zwei Substituenten H bedeuten, wobei der dritte Substituent gleich NH_2 oder $CONH_2$ ist.

Weiters werden erfindungsgemäß in vorteilhafter Weise Galanthaminderivate mit der allgemeinen Formel Ie

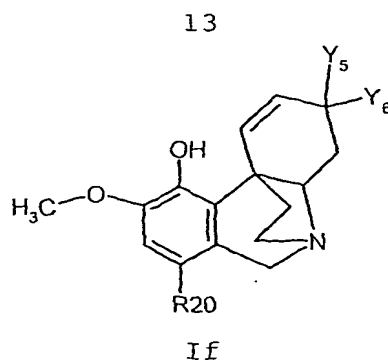


oder deren Salze verwendet, worin Z_4 ein geradkettiges oder verzweigte (C_1 - C_6) alkyl oder 4-brombenzyl ist.

Eine vorteilhafte Verwendung beruht erfindungsgemäß auf Basis von Galanthaminderivaten mit der allgemeinen Formel If

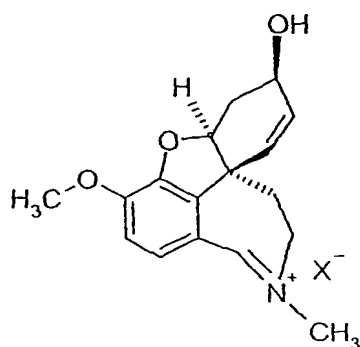
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oder deren Salzen, worin Y_5 und Y_6 die vorgenannten Bedeutungen haben und R_{20} gleich H oder Br ist.

Besonders vorteilhaft ist die Verwendung eines Galanthamin-derivates mit folgender Strukturformel

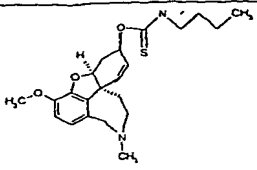
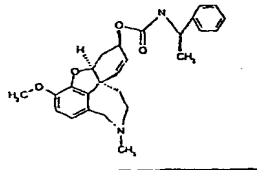
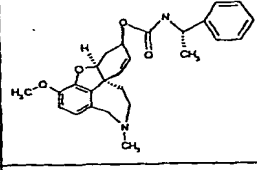
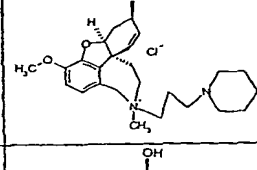
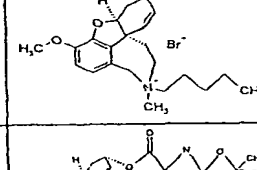
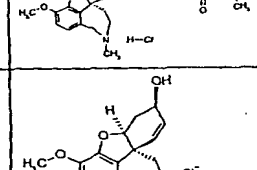
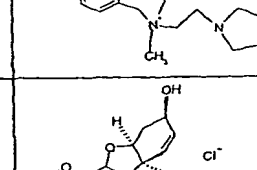
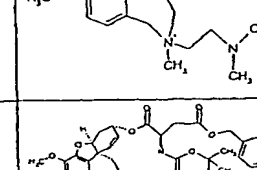
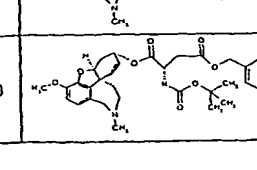



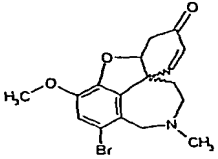
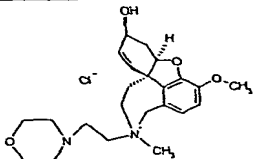
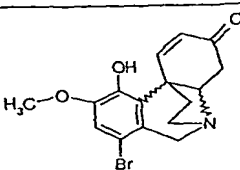
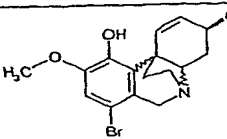
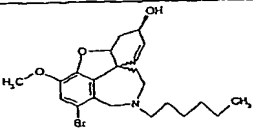
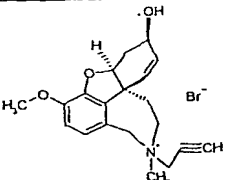
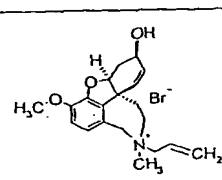
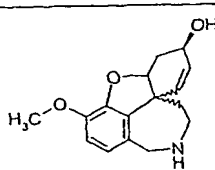
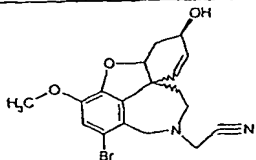
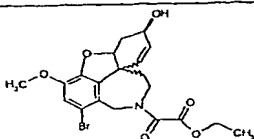
und mit der Bezeichnung (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-f][2]benzazepinium sowie seiner pharmazeutisch akzeptablen Salze, Hydrate oder Solvate.

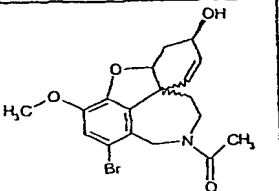
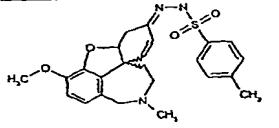
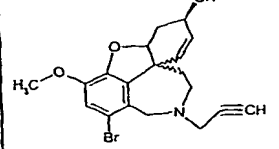
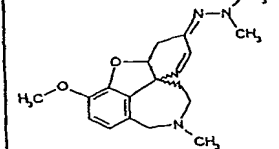
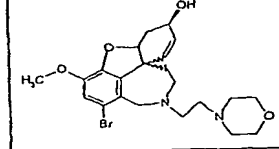
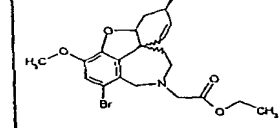
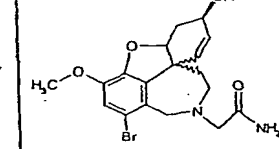
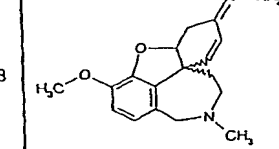
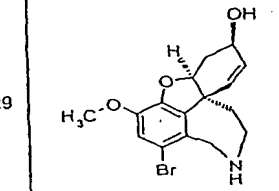
Als Gegenionen der pharmazeutisch akzeptablen Salze von (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium werden vorteilhafterweise Halogenide, vorzugsweise Bromid, sowie Carbonsäuren mit 1-3 Carboxylfunktionen, wobei Tartrate, Malonate, Fumarate und Succinate besonders bevorzugt sind, sowie Sulfonsäuren, vorzugsweise Methansulfonsäure, ausgewählt.

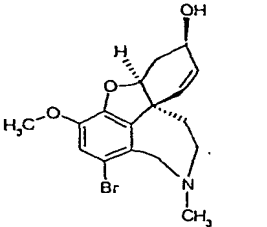
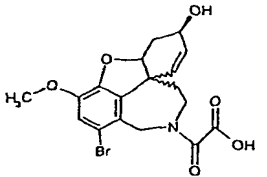
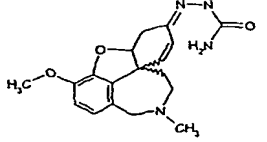
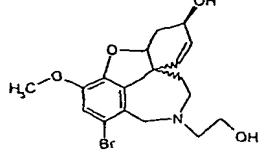
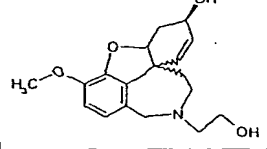
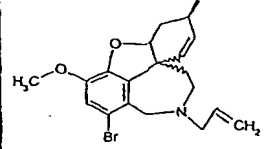
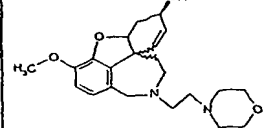
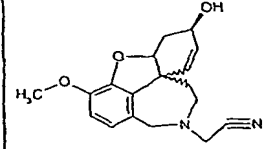
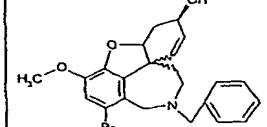
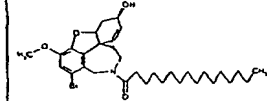
Das erfindungsgemäß verwendete Galanthamin sowie die erfindungsgemäß verwendeten Galanthaminderivate können nach den Verfahren, wie sie in den WO 96/12692 A, WO 97/40049 und WO 01/74820 geoffenbart sind, hergestellt werden.

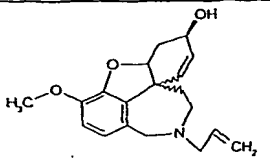
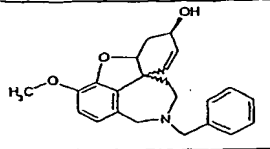
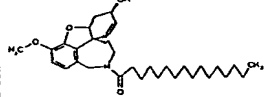
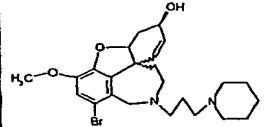
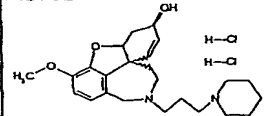
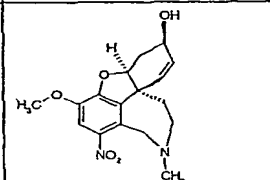
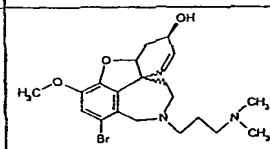
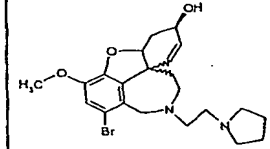
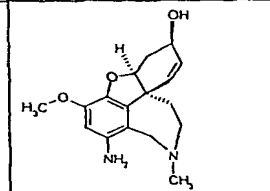
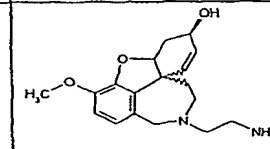
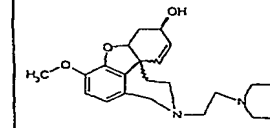
Für die Erfindung wesentlich ist die cholinerge Aktivität von Galanthamin und seinen Derivaten, wobei diese Eigenschaft dahingehend zu präzisieren ist, dass die erfindungsgemäß verwendeten Verbindungen die cholinolytische Wirkung von Cholinesterasen hemmen. Diese Eigenschaft kann - wie anhand folgender Tabelle gezeigt wird - an den auf 50% durch Inhibition gesenkten Konzentrationswerten für Acetyl- bzw. Butyrylcholinesterase nachgewiesen werden.

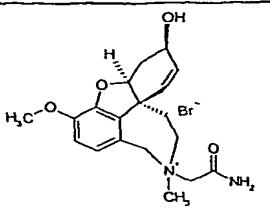
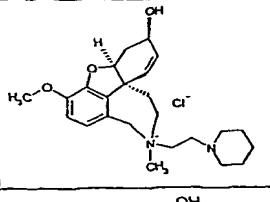
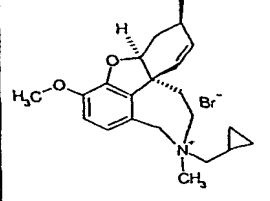
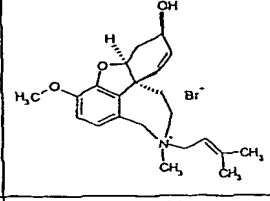
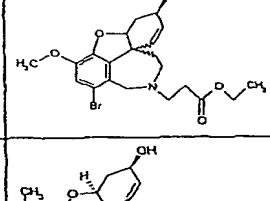
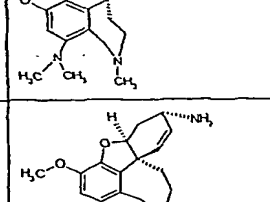
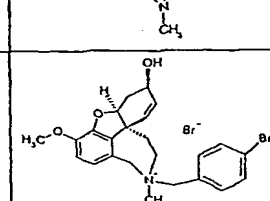
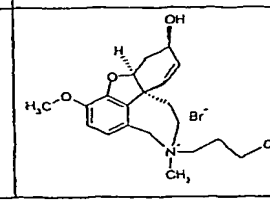

Nr	STRUCTURE	stereo	Acetyl- cholinesterase IC-50 (μM)	Butyryl- cholinesterase IC-50 (μM)
1		(-)	>100	4,8
2		(-)		70
3		(-)		75
4		(-)	6	
5		(-)		
6		(-) epi	45	
7		(-)	2	
8		(-)	8	
9		(-) epi		
10		(-) epi		

11		(-/+)	50	
12		(+)	57	13
13		(-/+)	5	
14		(-/+)	>100	18
15		(-/+)	40	0,45
16		(-)	1,4	1,7
17		(-)		
18		(-/+)	7	
19		(-/+)	>100	70
20		(-/+)	32	11

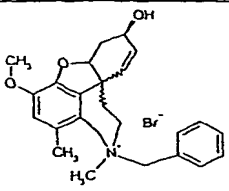
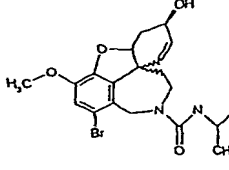
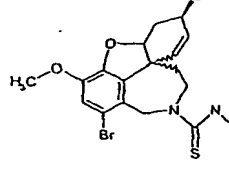
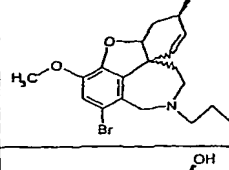
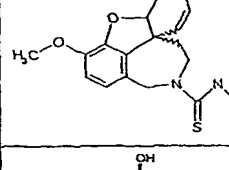
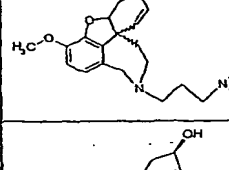
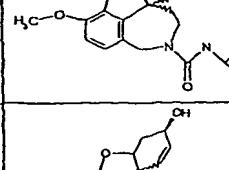
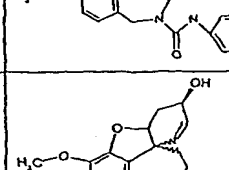
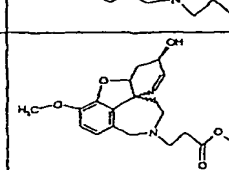

21		(-/+)		
22		(-/+)		
23		(-/+)	63	10
24		(-/+)	80	60
25		(-/+)	3	
26		(-/+)	20	
27		(-/+)	>100	15
28		(-/+)	40	
29		(-)	3	

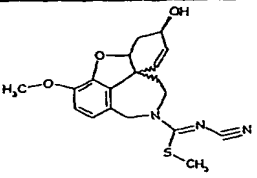
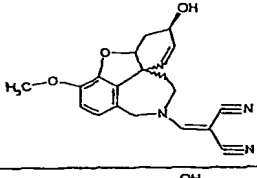
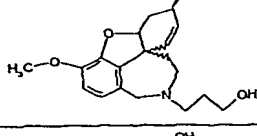
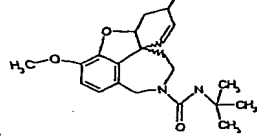
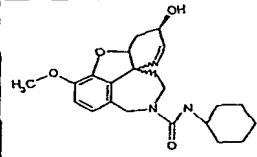
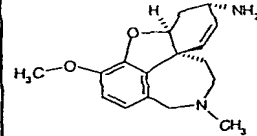
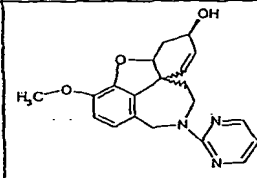
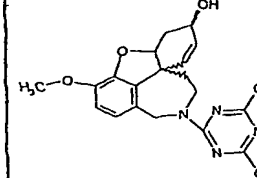
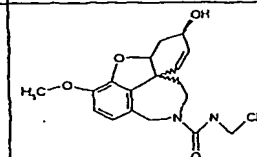
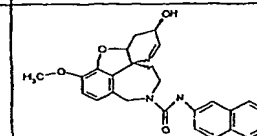
30		(-)	4	
31		(-/ +)		
32		(-/ +)	>100	20
33		(-/ +)	34	6,4
34		(-/ +)	14	26
35		(-/ +)	>100	2,6
36		(-/ +)	13	7
37		(-/ +)	30	>100
38		(-/ +)	>100	0,24
39		(-/ +)		

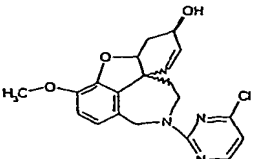
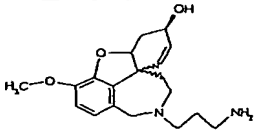
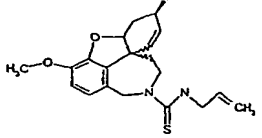
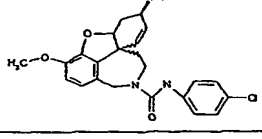
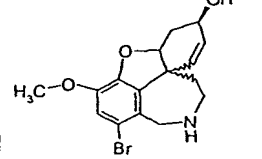
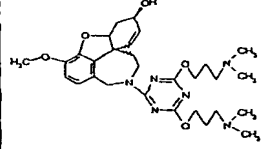
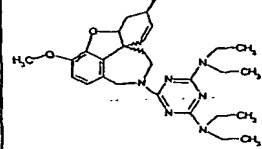
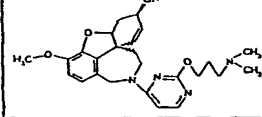
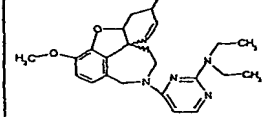
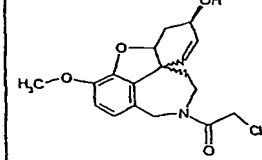
40		(-/+)	3,3	3,1
41		(-/+)	0,7	0,65
42		(-/+)		
43		(-/+)	0,2	
44		(-/+)		
45		(-)	>100	25
46		(-/+)		
47		(-/+)		
48		(-)	77	4,9
49		(-/+)		
50		(+/-)		

51		(-)	3,1	2,5
52		(-)	4	
53		(-)	1,2	3,6
54		(-)	0,2	0,21
55		(-/+)	>100	19
56		(-)	>100	0,47
57		(-) epi		
58		(-)	0,2	0,6
59		(-)	0,35	4,4

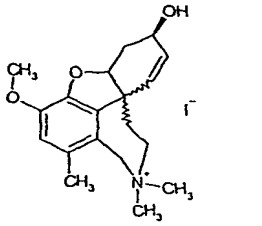
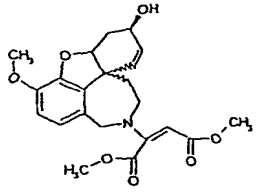
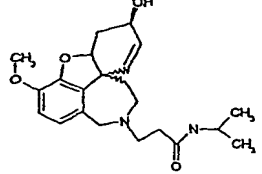
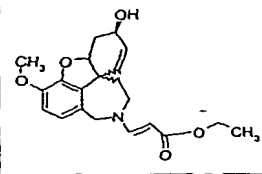
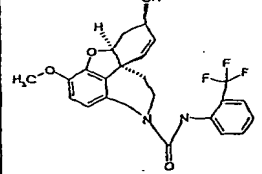
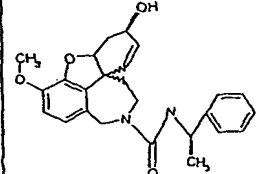
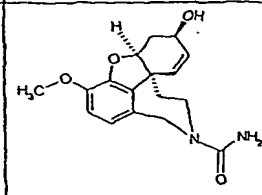
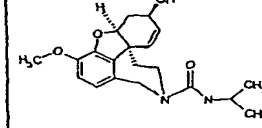
60		(-/+)	24	7,5
61		(-/+)	5,2	5
62		(-/+)	>100	2,3
63		(-/+)	>100	17
64		(-/+)	46	0,6
65		(-/+)	>100	5,2
66		(-/+)		
67		(-/+)	70	2,4
68		(-/+)	78	2,5

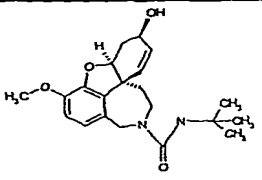
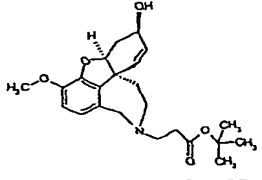
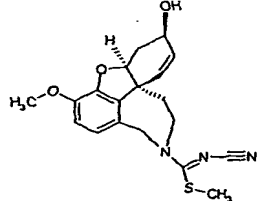
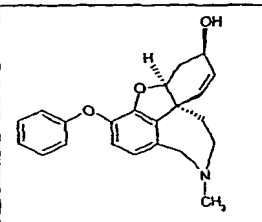
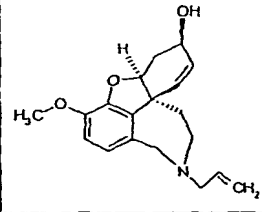
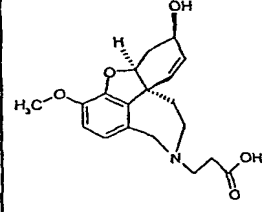
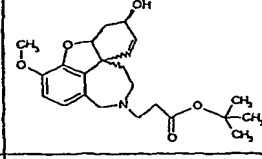
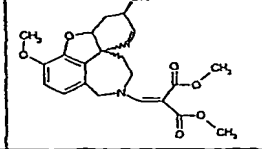
69		(-/+)	47	0,7
70		(-/+)	>100	25
71		(-/+)	31	20
72		(-/+)	>100	43
73		(-/+)	23	30
74		(-/+)	6	10
75		(-/+)	4,2	>100
76		(-/+)	70	>100
77		(-/+)	90	>100
78		(-/+)	9,5	17

79		(-/+)	25	0,54
80		(-/+)	28,5	>100
81		(-/+)	7,2	21
82		(-/+)	4,8	>100
83		(-/+)	6,7	>100
84		(-) epi	40	6
85		(-/+)	38	30
86		(-/+)		
87		(-/+)	33	>100
88		(-/+)	36	>100

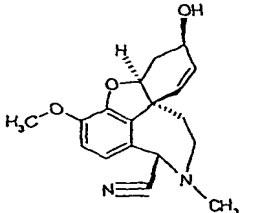
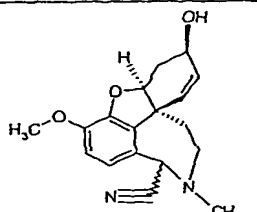
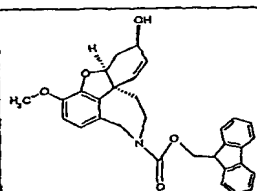
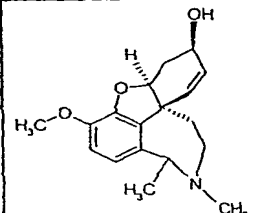
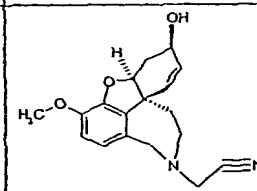
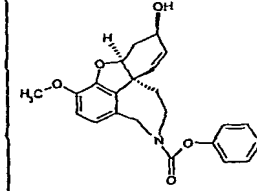
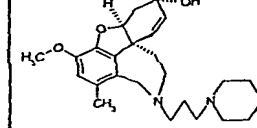
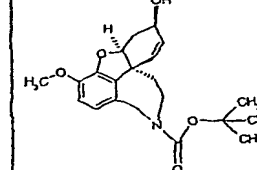
89		(-/+)	66	>100
90		(-/+)	3,4	11
91		(-/+)	21	>100
92		(-/+)	24	>100
93		(-/+)	5	
94		(-/+)	70	40
95		(-/+)	40	>100
96		(-/+)	7,4	36
97		(-/+)	25	>100
98		(-/+)	17,5	20

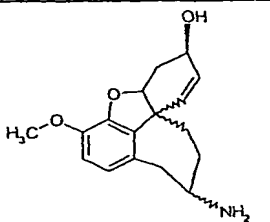
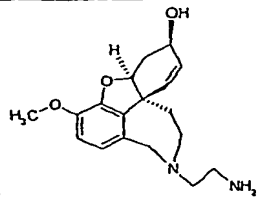
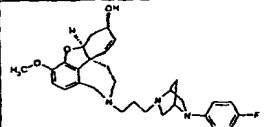
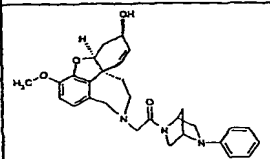
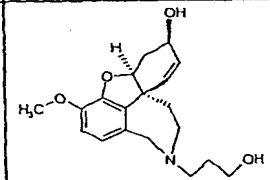
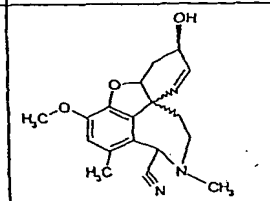
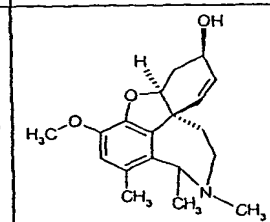
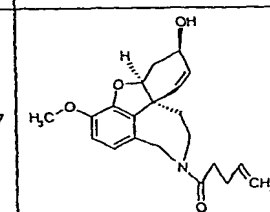
99		(-)	2,4	4
100		(-/+)	40	90
101		(-/+)	45	26
102		(-/+ epi)	>100	95
103		(-/+ epi)	59	45
104		(-/+ epi)	>100	52
105		(-/+ epi)	60	5,4
106		(-/+ epi)	>100	3

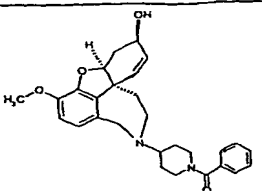
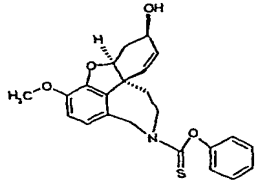
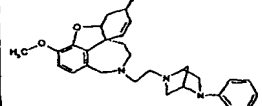
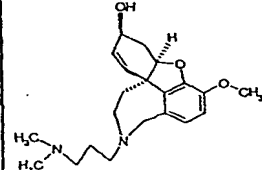
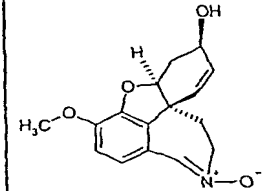
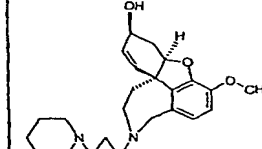
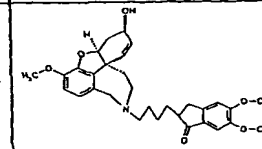
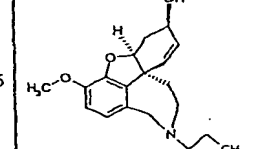
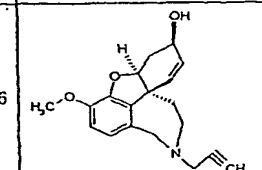
107		(-/+)	>100	14
108		(-/+)	140	80
109		(-/+)	54,5	36
110		(-/+)	50	>100
111		(-)	30	>100
112		(-/+)	30	>100
113		(-)	44	>100
114		(-)	2,6	10

115		(-)	2,5	7
116		(-)	15	4
117		(-)	6,7	30
118		(-)	21	3,4
119		(-)		
120		(-)	42	40
121		(-/+)	33	7,3
122		(-/+)	100	32

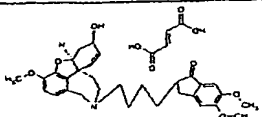
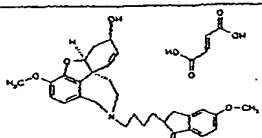
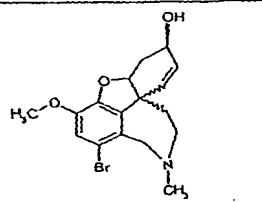
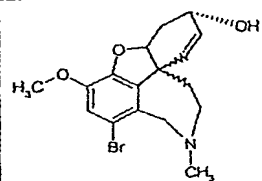
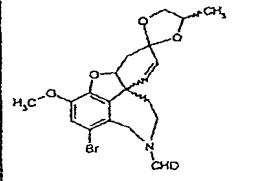
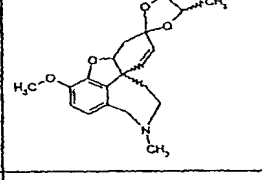
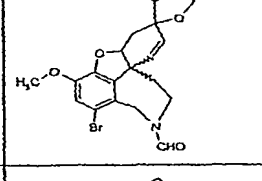
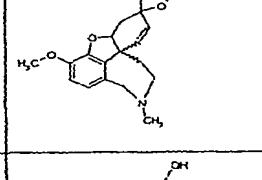
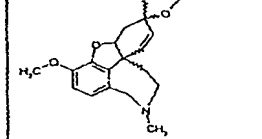
123		(-)	0,5	0,24
124		(-)	4	0,54
125		(+)	93	100
126		(+)	8	90
127		(-)	0,3	1,5
128		(-)	0,3	1,5
129		(-)	18,5	63
130		(-)	6,3	60
131		(-)	0,7	1,2

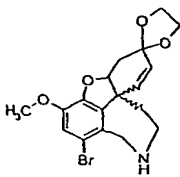
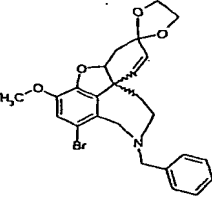
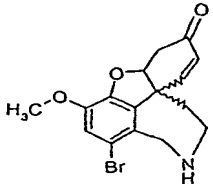
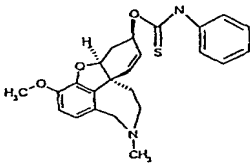
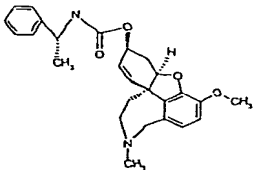
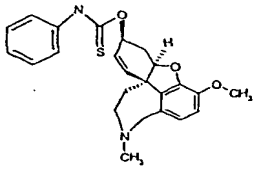
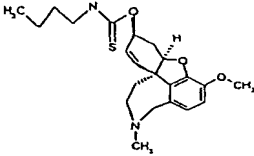
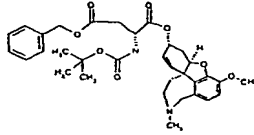
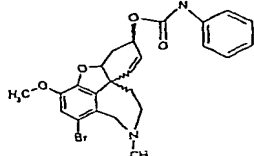
132		(-)	1,2	100
133		(-)	0,8	>100
134		(-)	40	100
135		(-)	4,2	25
136		(-)	15	32
137		(-)	46	>100
138		(-) epi	>100	70
139		(-)	23	>100

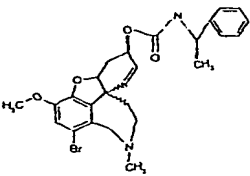
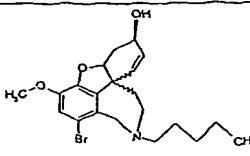
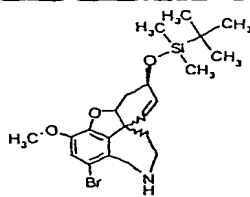
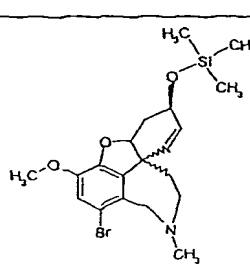
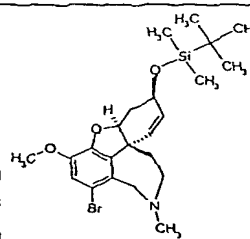
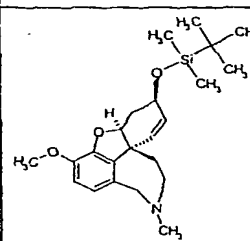
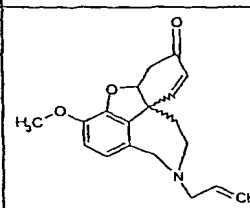
140		(+/-)	5,3	>100
141		(-)	1,3	2,1
142		(-)	3	2,4
143		(-)	8,4	2,4
144		(-)	2,8	5
145		(+/-)	80	>100
146		(-)	83	30
147		(-)	8,4	2,6

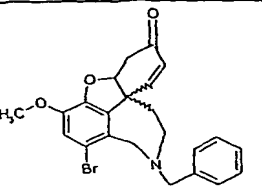
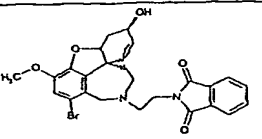
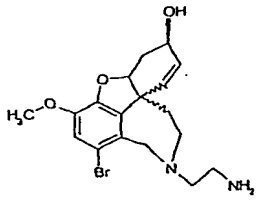
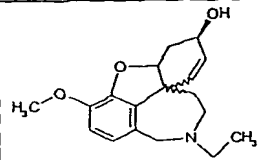
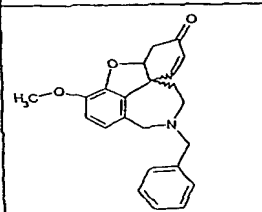
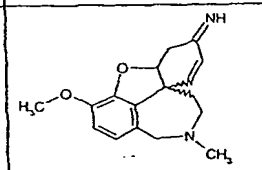
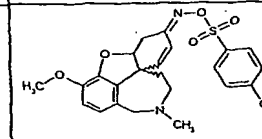
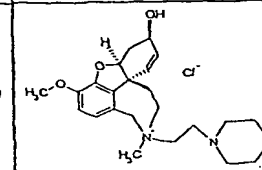
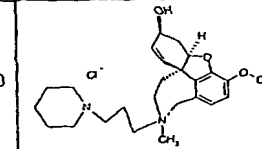
148		(-)	24	3
149		(-)	7,2	>100
150		(-)	2,9	0,85
151		(+)	64	67
152		(-)	50	>100
153		(+)	9	23
154		(-)	0,02	0,8
155		(-)	0,3	1,5
156		(-)	32	30

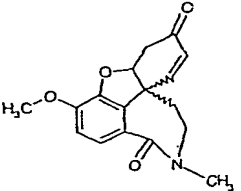
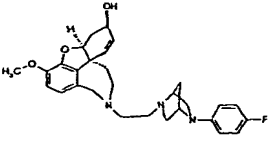
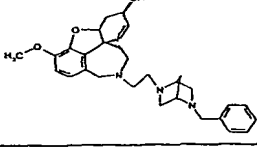
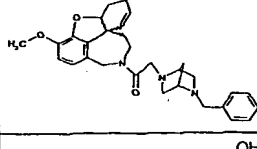
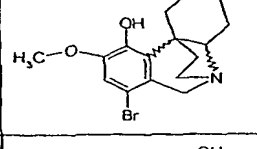
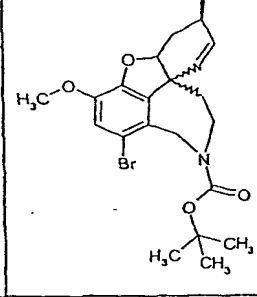
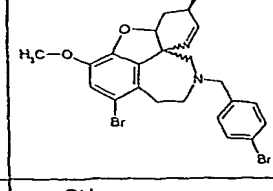
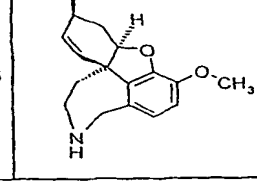
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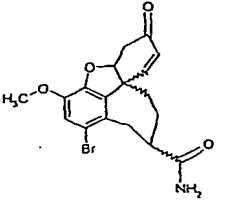
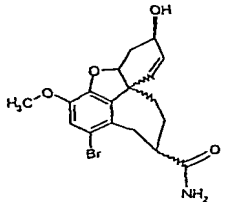
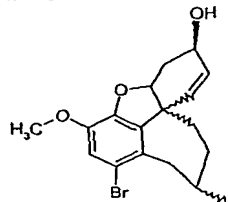
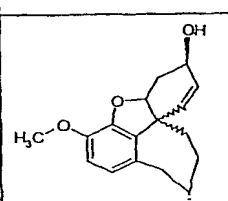
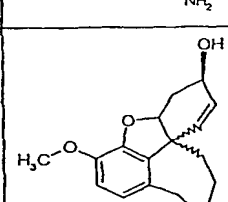
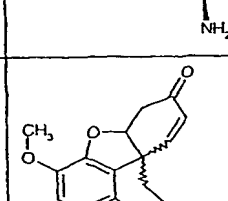
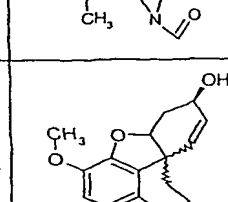
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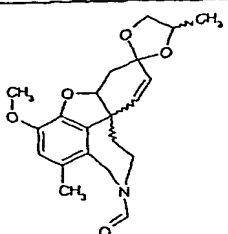
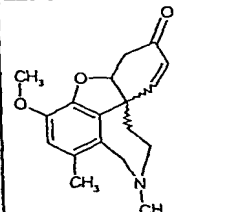
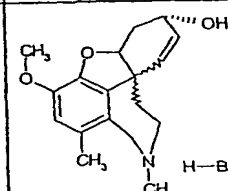
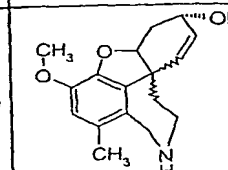
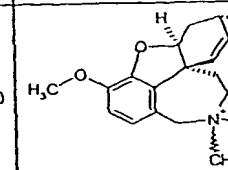
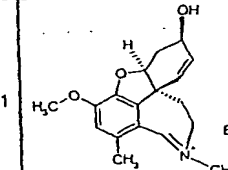
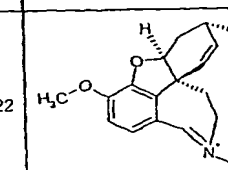
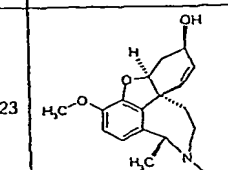
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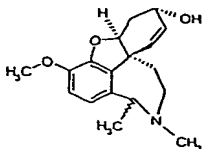
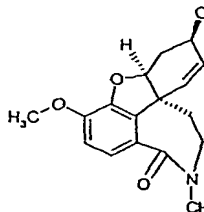
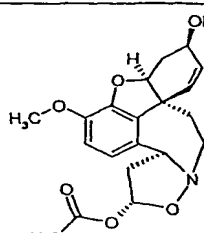
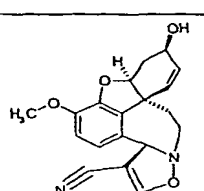
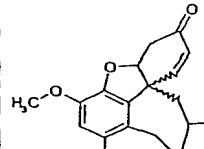
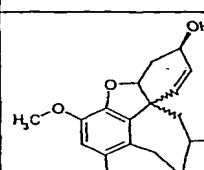
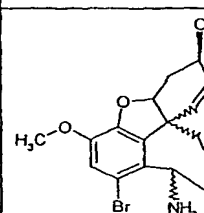
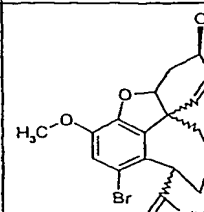
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194		(+/-)		
195		(+/-)		
196		(+/-)		
197		(+/-)		
198		(+/-)		
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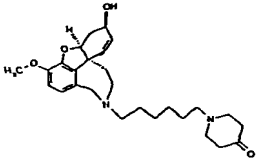
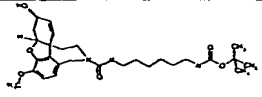
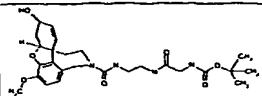
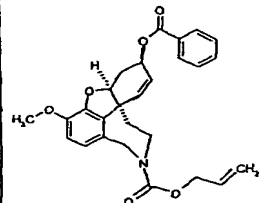
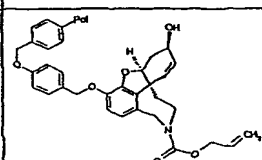
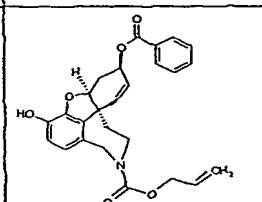
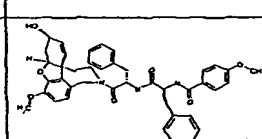
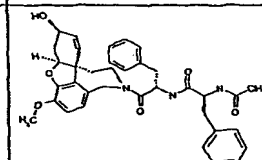
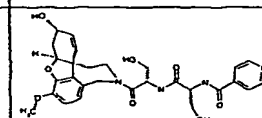
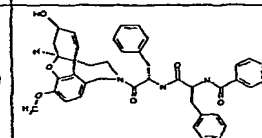
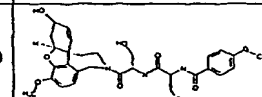
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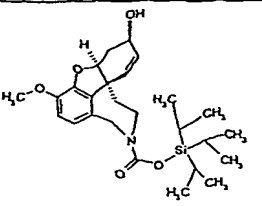
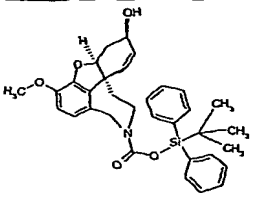
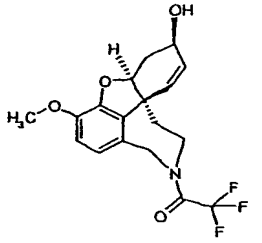
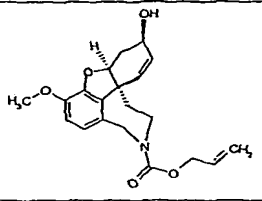
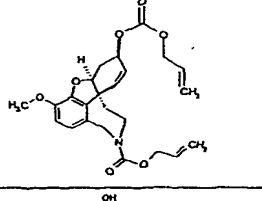
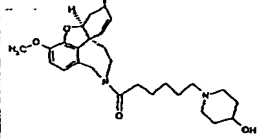
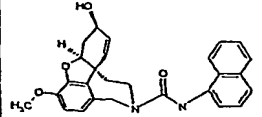
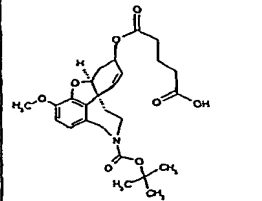
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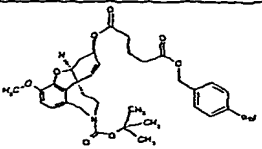
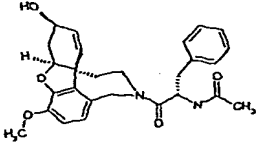
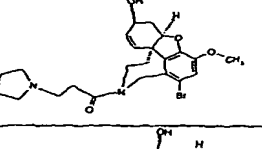
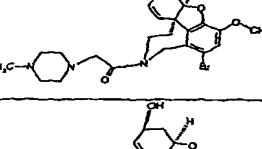
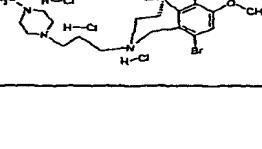
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261		(-)		
262		(-)		
263		(-)		
264		(-)		
265		(-)		
266		(-)		
267		(-)	70	>100
268		(-)		

269		(-)		
270		(-)		
271		(+)	>100	66
272		(+)	89	> 100
273		(+)	> 100	31

Da aus den Messwerten gemäß Tabelle der Nachweis für cholinerge Aktivität, präziser für die cholinolytische Wirkung von Cholinesterasen hemmende Eigenschaft erbracht werden kann, werden aus diesen chemischen Verbindungen Arzneimittel für die Behandlung sowie für die präventive Behandlung von postoperativem Delir und/oder subsyndronalem postoperativem Delir hergestellt.

Die unter Verwendung von Galanthamin und seinen Derivaten erhältlichen Arzneimittel können auch einen Wirkstoff oder eine Kombination von Wirkstoffen enthalten. Unter Kombination werden auch Kombinationen der erfindungsgemäß in Betracht gezogenen Verbindungen mit anderen pharmazeutisch aktiven Substanzen verstanden.

Es wurde nunmehr festgestellt und durch eine umfangreiche klinische Studie erhärtet, dass orale Verabreichung von Galanthamin (in Form des unter dem Markennamen Reminyl® zur Therapie der leichten bis mittelschweren Alzheimer'schen Krankheit handelsüblichen Hydrobromids) an präoperativ nicht demente oder kognitiv eingeschränkte Patienten mit akutem POD eine bisher nicht beschriebene, unerwartet schnelle und weitgehende Besserung der Symptome bewirkt. Als besonders überraschend muss dabei herausgestrichen werden, dass die beobachteten Nebenwirkungen der Galanthamin-Verabreichung sehr gering waren, obwohl postoperative Patienten erfahrungsgemäß eine erhöhte cholinerge Sensitivität aufweisen.

Dies soll anhand folgender Anwendungsbeispiele näher erläutert werden:

Beispiel 1:

Die Verabreichung von Galanthamin oder seinen pharmakologisch akzeptablen Salzen und Solvaten zur Therapie oder Prophylaxe des postoperativen Delirs kann oral (in Form von Tabletten, Kapseln, Trinklösungen oder buccalen Tabletten), intravenös, rektal (in Form von Suppositorien) oder transdermal (in Form von passiv oder aktiv Galanthamin durch die Haut abgebenden Systemen) erfolgen.

Eine bevorzugte Form der Verabreichung erfolgt oral, wobei ein beispielhaftes Verabreichungsschema zur Prophylaxe des Postoperativen Delirs darin besteht, dass am Abend nach dem chirurgischen Eingriff 8 mg Galanthamin hydrobromid in Form von den Wirkstoff direkt freisetzenden Tabletten oder Trinklösungen verabreicht werden. An den vier auf den Operationstag folgenden Tagen werden morgens und mittags je 4 mg, sodann am Abend 8 mg

verabreicht. Am fünften postoperativen Tag werden morgens und mittags jeweils 4 mg verabreicht und die Prophylaxe sodann beendet. Es versteht sich für den Fachmann von selbst, dass diese Dosierungen an das Körpergewicht des Patienten, dessen Allgemeinzustand usw. angepasst werden können.

Galanthamin hydrobromid enthaltende Tabletten mit direkter Freisetzung des Wirkstoffes, die sich erfindungsgemäß für diese Art der Verabreichung eignen, sind unter dem Handelsnamen Reminyl® zur Therapie der Alzheimer'schen Krankheit zugelassen.

Galanthamin enthaltende Trinklösungen, die sich erfindungsgemäß für diese Art der Verabreichung eignen, sind in WO-0130318 beschrieben, wobei eine solche Trinklösung in beispielhafter Weise wie folgt zusammengesetzt sein kann:

Galanthamin HBr	5,124 mg
Methyl 4- hydroxbenzoate	1,8 mg
Propyl 4- hydroxybenzoate	0,2 mg
Natriumsaccharat dihydrat	0,5 mg
Wasser (pH 4.9 -5.1)	1,0 ml

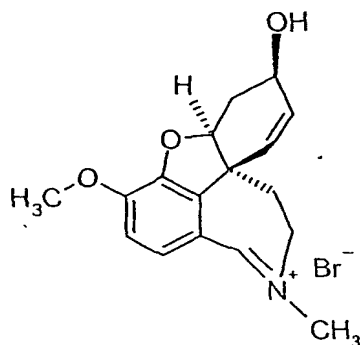
Ein weiteres orales Verabreichungsschema verwendet Kapseln mit verzögerter Wirkstofffreisetzung, wobei am Abend nach dem chirurgischen Eingriff 8 mg Galanthamin hydrobromid und an den darauf folgenden vier Tagen mittags oder abends jeweils 8 mg verabreicht werden. Mehrere Ausführungen erfindungsgemäß verwendbarer Kapseln mit verzögerter Wirkstofffreisetzung sind im Dokument WO 0038686 beschrieben, auf das hier zur Gänze Bezug genommen wird.

Eine weitere bevorzugte erfindungsgemäße Darreichungsform ist transdermal, wobei sich die in WO-9416707 beschriebenen passiven transdermalen Systeme in besonderer Weise eignen. In diesem Fall wird ein derartiges transdermales Pflaster, das im Verlauf von 24 Stunden ca. 10 mg Galanthamin-Base freisetzt, unmittelbar nach dem Aufwachen aus der Narkose appliziert und an den nächsten vier Tagen jeweils durch ein neues Pflaster ersetzt; am fünften Tag erfolgt keine erneute Applikation mehr.

Selbstverständlich sind Kombinationen von verschiedenen hier beschriebenen Darreichungswegen möglich. Insbesondere erweist es sich als nützlich, die transdermale Darreichung zum schnelleren Wirkungseintritt am Abend des Operationstages durch einmalige orale Gabe von 4 mg Galanthamin HBr (als direkt freisetzen- de Tablette oder Trinklösung) zu unterstützen.

Beispiel 2:

Die Verabreichung von (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium Verbindungen erfolgte beispielsweise mit Bromid als Gegenion. Dabei handelt es sich um ein Galanthaminderivat mit folgender Strukturformel:



Es ist jedoch auch möglich, die Verabreichung mittels pharmakologisch akzeptablen Hydraten und Solvaten vorzunehmen. Die Therapie oder Prophylaxe des postoperativen Delirs kann oral (in Form von Tabletten, Kapseln, Trinklösungen oder buccalen Tabletten), intravenös, rektal (in Form von Suppositorien) oder transdermal (in Form von passiv oder aktiv die vorgenannte Verbindung durch die Haut abgebenden Systemen) erfolgen. Eine bevorzugte Form der Verabreichung erfolgt oral, wobei ein beispielhaftes Verabreichungsschema zur Prophylaxe des Postoperativen Delirs darin besteht, dass am Abend nach dem chirurgischen Eingriff 2-6 mg (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium Bromid in Form von den Wirkstoff direkt freisetzenden Tabletten oder Trinklösungen verabreicht werden. An den vier auf den Operationstag folgenden Tagen werden morgens und mittags jeweils 1-3 mg, sodann am Abend 2-6 mg verabreicht. Am fünften postoperativen Tag werden morgens und mittags jeweils 1-3 mg

verabreicht und die Prophylaxe sodann beendet. Es versteht sich für den Fachmann von selbst, dass diese Dosierungen an das Körpergewicht des Patienten, dessen Allgemeinzustand usw. angepasst werden können. Ebenso können anstelle des Bromids auch andere physiologisch akzeptable, leicht wasserlösliche Salze des Wirkstoffes (z.B. anderes Halogenid, Maleat, Tartrat) eingesetzt werden.

(4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium Bromid enthaltende Tabletten mit direkter Freisetzung des Wirkstoffes, die sich erfindungsgemäß für diese Art der Verabreichung eignen, können beispielsweise wie folgt zusammengesetzt und wahlweise mit pharmazeutisch akzeptablen Überzügen versehen sein:

(4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium Bromid	2,0 mg
Kalziumphosphat	25,0 mg
Laktose	5,0 mg
Weizenstärke	5,0 mg
Mikrokristalline Zellulose	40 mg
Talkum	2 mg
Magnesium Stearat	1,0

Der Fachmann wird aufgrund der für Galanthamin genannten Beispiele unter Anwendung üblicher galenischer Praktiken leicht ähnliche Darreichungsformen für (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium Bromid oder analogen Salzen, Hydraten oder Solvaten finden können.

Um die Wirkung der Darreichungsformen auch an Patienten testen zu können, wurde eine prospektive Studie zur Prävention des postoperativen Delir an fünf österreichischen orthopädischen Kliniken (zwei in Wien, je eine in Linz, Graz und Krems) an insgesamt 229 Patienten durchgeführt, die sich geplanten chirurgischen Eingriffen zur Implantation einer Hüft- bzw. kombinierten Hüft/Knie-Endoprothese unterzogen. Den Patienten der Verum-Gruppe

wurden an dem auf den Eingriff folgenden Abend (Tag 0) 8 mg Galanthamin HCl verabreicht, sodann an den Tagen 1 bis 4 jeweils 4 mg morgens und mittags und 8 mg abends, das heißt 16 mg t.i.d. Am 5. Tag nach dem Eingriff wurde die Dosis auf 8 mg b.i.d. reduziert, ab dem 6. Tag erfolgte keine Behandlung mehr. Patienten der Placebo-Gruppe erhielten nach dem gleichen Schema subjektiv nicht unterscheidbare Placebo-Tabletten.

Für die Bestimmung der Wirksamkeit mit Hilfe der „Confusion Assessment Method“ (Lit.14) konnten 155 Patienten herangezogen werden. In der Placebo-Gruppe entwickelten 7 Patienten (8,5%) ein postoperatives Delir, in der Galanthamin-Gruppe nur ein Patient (1,4%), was einem statistisch signifikanten Unterschied ($p=0,044$) entspricht.

Die Auswertung der Studie zeigt somit in eindeutiger Weise die Wirksamkeit von Galanthamin bei Postoperativem Delir.

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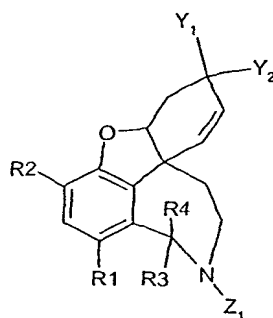
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Patentansprüche:

1. Verwendung von Galanthamin und seinen cholinerge Aktivität aufweisenden Derivaten zum Herstellen von Arzneimitteln zur Behandlung von postoperativem Delir und/oder subsyndronalem postoperativem Delir.

2. Verwendung nach Anspruch 1 zum Herstellen von Arzneimitteln zur präventiven Behandlung von postoperativem Delir und/oder subsyndronalem postoperativem Delir.

3. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die verwendeten Galanthamin-derivate Verbindungen mit der allgemeinen Formel Ia



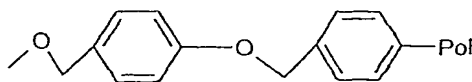
Ia

oder deren Salze sind, worin

- R_1 gleich H, verzweigtes oder geradkettiges (C_1-C_6) alkyl, Br, NO_2 , NR_5R_6 ist,
- R_5 und R_6 gleich oder verschieden sind und H, verzweigtes oder geradkettiges (C_1-C_6) alkyl bedeuten,

und worin

- R_2 gleich OH, verzweigtes oder geradkettiges (C_1-C_6) alkyl, methoxy, phenyloxy ist oder folgende Gruppe

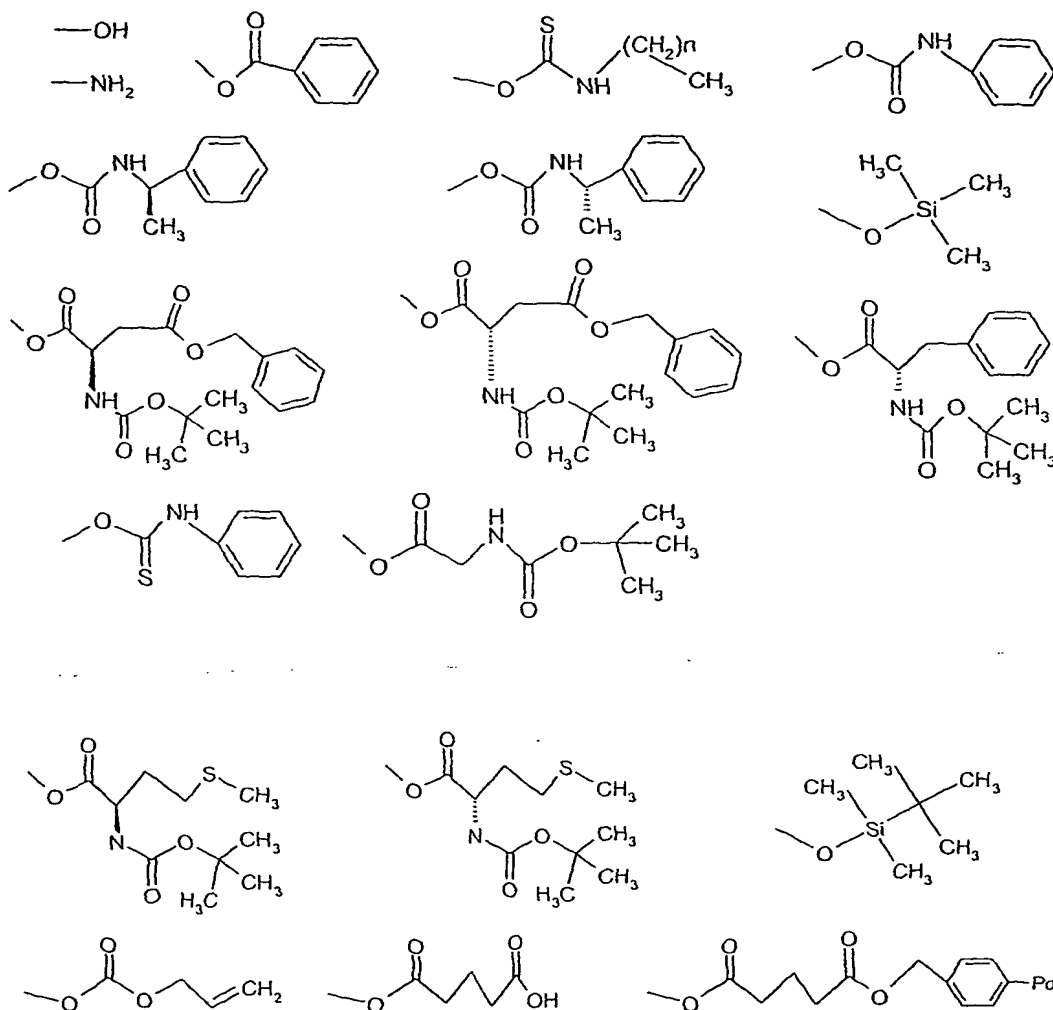


bedeutet, wobei Pol ein Polymer, vorzugsweise eines gemäß WO-A1-01/174820 ist, und worin

- R_3 und R_4 entweder gleichzeitig oder wechselweise H, D, CN, geradkettiges oder verzweigtes (C_1 - C_6) alkyl oder gemeinsam eine Carbonylgruppe bedeuten,

worin weiters

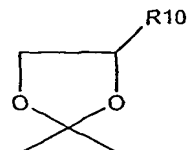
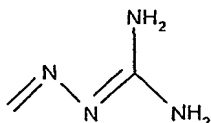
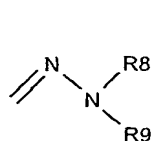
- Y_1 und Y_2 wechselweise H oder eine Gruppe ausgewählt aus:



sind, wobei n einen Wert von 0, 1 bis 15 darstellt, und Pol die oben angegebene Bedeutung hat, und wobei weiters

o Y_1 und Y_2 gemeinsam eine Carbonylgruppe ($=O$), $=NH$, $=N-OR_7$, darstellen, wobei R_7 gleich H, Tosyl oder verzweigtes oder geradkettiges (C_1-C_6) alkyl ist,

o oder Y_1 und Y_2 gemeinsam eine Gruppe ausgewählt aus :

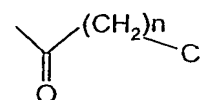
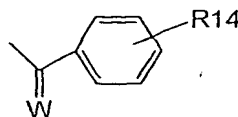
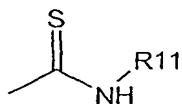
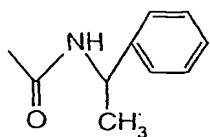
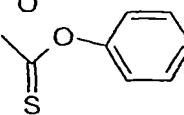
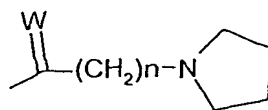
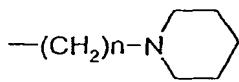
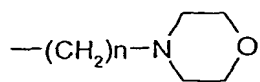
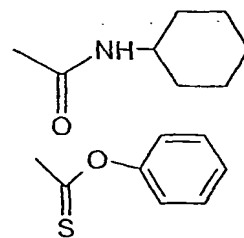
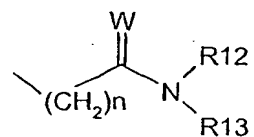
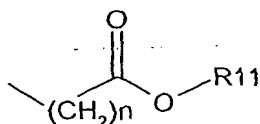
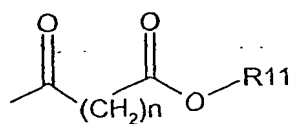


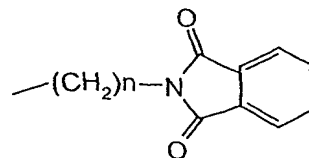
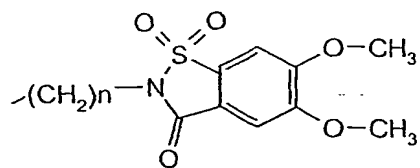
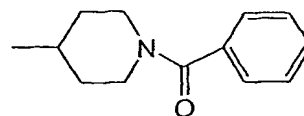
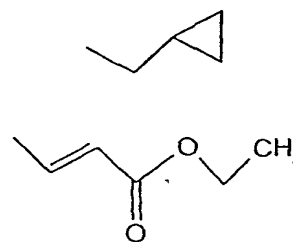
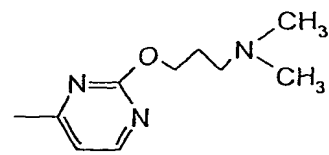
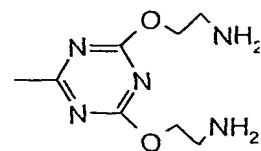
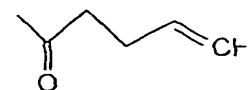
bilden, wobei R_8 und R_9 gleich oder verschieden sind und H, verzweigtes oder geradkettiges (C_1-C_6) alkyl, $-(CH_2)_2-OH$, CHO , $CONH_2$, tBOC (terc. Butoxycarbonyl), oder $-COCOOH$ bedeuten, R_{10} gleich H oder CH_3 ist, und wobei für Y_1 gleich $-O-(CH_2)_2-OH$ Y_2 gleich OH ist,

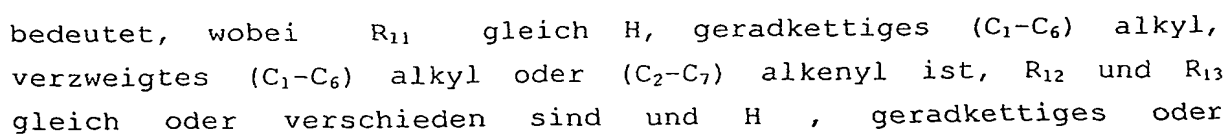
und worin

- Z_1 gleich H, verzweigte oder geradkettiges (C_1-C_6) alkyl, (C_2-C_7) alkenyl (C_2-C_7) alkynyl, trifluoracetyl, formyl, phenyl

oder eine Gruppe ausgewählt aus:



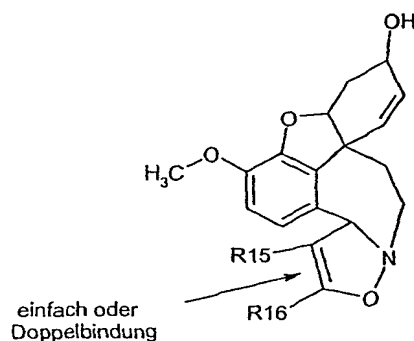




verzweigtes (C_1-C_6) alkyl, phenyl, chlorphenyl, (trifluormethyl)-phenyl oder 1-naphtyl bedeuten, wobei R_{14} gleich H, F, CH_3 , NO_2 , Cl, Br, J, CF_3 ist, n die oben angegebene Bedeutung hat, m gleich 0 oder 1 ist, und W die Bedeutung H oder O hat,

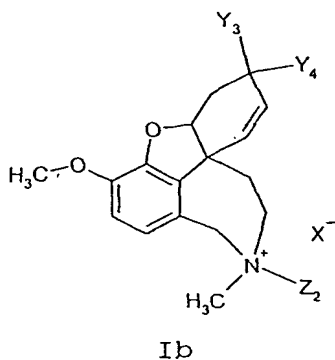
und worin weiters

- Z_1 und R_3 einen gemeinsamen Ring



bilden, wobei R_{15} und R_{16} wechselweise H, $COOCH_3$, $COOCH_2CH_3$, CN, $COCH_3$ bedeuten.

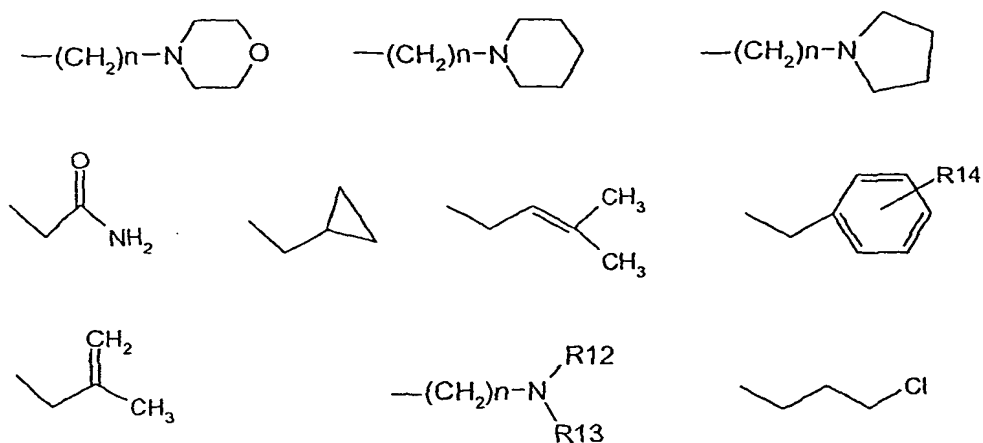
4. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die verwendeten Galanthaminderivate Verbindungen mit der allgemeinen Formel Ib



sind, worin

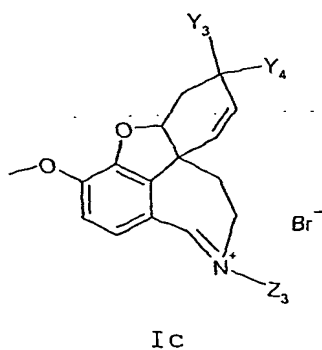
- Y_3 und Y_4 wechselweise H und OH bedeuten,

- X gleich Cl, Br oder I ist,
- Z₂ gleich Sauerstoff (N-Oxyd und kein Gegenion), verzweigtes oder geradkettiges (C₁-C₆) alkyl, oder (C₂-C₇) alkenyl oder (C₂-C₇) alkynyl oder eine Gruppe ausgewählt aus:



bildet, wobei n, R₁₂, R₁₃ und R₁₄ die Bedeutung gemäß Anspruch 3 haben.

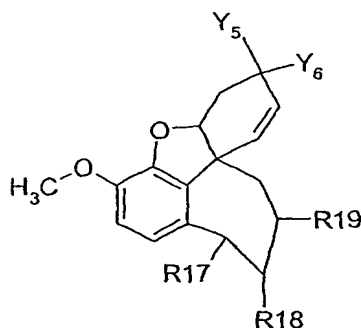
5. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die verwendeten Galanthaminderivate Verbindungen mit der allgemeinen Formel Ic



sind, worin

- Y₃ und Y₄ die Bedeutung gemäß Anspruch 3 oder 4 hat, und
- Z₃ gleich Sauerstoff (N-Oxyd und kein Gegenion) oder eine Methylgruppe ist.

6. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die verwendeten Galanthaminderivate Verbindungen mit der allgemeinen Formel Id

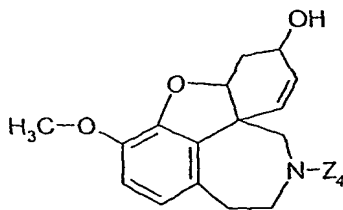


Id

oder deren Salze sind, worin

- Y_5 und Y_6 wechselweise H oder OH bedeuten oder gemeinsam eine Ketogruppe bilden, und
- R_{17} , R_{18} , R_{19} wechselweise für je zwei Substituenten H bedeuten, wobei der dritte Substituent gleich NH_2 oder $CONH_2$ ist.

7. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die verwendeten Galanthaminderivate Verbindungen mit der allgemeinen Formel Ie

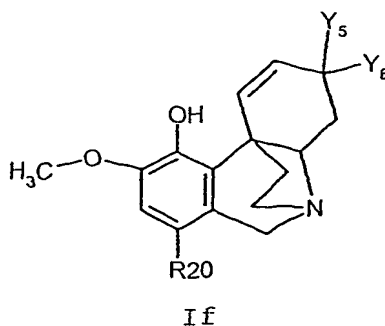


Ie

oder deren Salze sind, worin

- Z_4 geradkettiges oder verzweigtes (C_1-C_6) alkyl oder 4-brombenzyl ist.

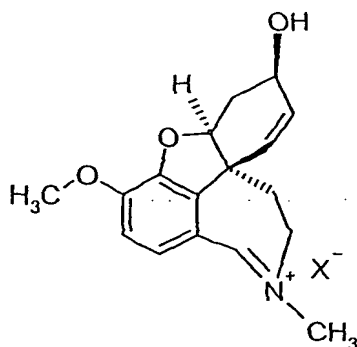
8. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die verwendeten Galanthaminderivate Verbindungen mit der allgemeinen Formel If



oder deren Salze sind, worin

- Y₅ und Y₆ die Bedeutungen nach einem der Ansprüche 3 bis 7 hat und
- R₂₀ gleich H oder Br ist.

9. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass das verwendete Galanthaminderivat folgende Strukturformel



aufweist und ein pharmazeutisch akzeptables Salz, Hydrat oder Solvat von (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-f][2]benzazepinium ist.

10. Verwendung nach Anspruch 9, dadurch gekennzeichnet, dass die Gegenionen des pharmazeutisch akzeptablen Salzes von (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium aus der Gruppe der Halogenide, vorzugsweise Bromid, der Carbonsäuren mit 1-3

Carboxylfunktionen, wobei Tartrate, Malonate, Fumarate und Succinate besonders bevorzugt sind, sowie Sulfonsäuren, vorzugsweise Methansulfonsäure, ausgewählt sind.

Use of Galanthamine and the Derivatives Thereof in the Production of Medicaments

The present invention relates to the use of galanthamine and
5 galanthamine derivatives for manufacturing medicaments useful
for the treatment of post-operative delirium.

Despite clear progress in the field of anesthesia as well as
in the perioperative time, today a substantial portion of the
patients, having large surgical procedures and interventions,
10 suffer from post-operative psychiatric complications, more in
particular this psychiatric complications fall broadly under the
umbrella of post-operative delirium.

Delirium is a medical condition of disturbed consciousness,
characterized by general confusion, reduction of cognitive
15 functions (attention, concentration and memory), hallucinations
and unstable emotions. Thus, delirium exhibits elements of
dementia like other psychotic conditions, however it is
distinguished from those conditions particularly by its acute
nature and usually occurs spontaneously, even if often delayed and
20 incomplete it is reversible.

Contrary to the degenerative dementia syndromes even when
they are present and excluding functional disturbances of the
central nervous system with post-operative delirium, the clinical
picture produced by the individual psychiatric symptoms can
25 fluctuate very fast - occasionally within seconds -.

Acute or subacute delirium (according to the medical
classifications ICD 293.0 and/or 293.1 of the World Health
Organisation) is often induced by intake or administration of
pharmacologically effective substances. Numerous such substances
30 are active substances or metabolites of medicines, so that a
medicament-induced delirium (ICD 292.81) can arise. In particular
medicines with an anti-cholinergic effect, which partly block the
nervous system based on the neurotransmitter acetyl choline, can
induce a delirium, however sedatives, like benzodiazepines, and
35 antimaniacals such as lithium salts can also induce delirium.

Also intoxicants and/or their acute withdrawal after chronic
use can produce delirium. This occurs very frequently especially
with acute alcohol abuse and/or in the case of alcohol withdrawal
(ICD 291.0). However substances such as Cannabis, Amphetamine,
40 cocaine etc. can also cause delirious conditions.

While the consciousness changes associated with a state of delirium mentioned above have a neurochemically directly comprehensible cause, there is also in the long run an unknown genesis for delirium. Also, despite the well-known techniques
5 (surgical interventions) there is no doubt that one has to deal with post-operative delirium, since there may not be a basis for a pathological mechanism.

Post-operative delirium (POD) is regarded today as a multi-functional syndrome (1), whereby the age and the general state of
10 health of the patient play a role, like possibly in preoperative existing cognitive disturbances, which may be influenced by the given defined anesthetic, and possibly also determined by intraoperative physiological changes (2). Although POD can occur immediately after awaking from the anesthetic provided, it is not
15 to be equated with fast disorientation occurring after anaesthesia. Rather POD can also begin on the second post-operative day or also still later, after actual awakening or coming out from the given anesthesia after running its clinical course. Thus a direct effect of the perioperative given
20 anesthetic and/or analgesics is to be excluded in these cases.

Although the scientific literature has contradictory data concerning the incidence of POD (which to a large extent points up to differences in the examined patient populations and the used psychiatric definition that is leading back to it), there exists
25 nevertheless general agreement that it concerns a quite frequently arising phenomenon (3), in particular after large orthopedic surgical interventions (4) and particularly with older patients. A recently published study (5) found using the clinically very relevant and valid Confusion Assessment Method (CAM; 6) that of
30 2158 post-operative patients, 16% fully hinted at having delirium, 13% with at least two key symptoms, and 40% with at least one symptom, while only 32% were symptom-free.

Although POD arises thus frequently and almost exclusively with stationary or bedridden patients, and although it is
35 considered as a bad prognostic indication to the further post-operative process, this condition is frequently not noticed or is not considered. This is to be attributed above all to the fact that post-operative patients usually remain under the supervision of the responsible surgical departments and that because of their
40 apathy and stress (hypoactive) the personnel often do not

recognize delirium. Only behavior-remarkable (hyperactive) patients are treated therapeutically with antipsychotics and/or sedatives (7). Already the therapy of the so-called subsyndromes of POD (which do not fulfill the psychometrics criteria of POD) would be extremely important, since its existence represents a risk factor for the progression and the time-frame of the delirious condition, and to what is statistically seen with an extended hospital stay, such as increased mortality after dismissal, and with later controlled investigations accompanies a decreased cognitive achievement (8); with the latter sequences one also speaks of Post-Operative Cognitive Decline (POCD), which condition can change into dementia.

The use of cholinesterase inhibitors for the therapy of medicament-induced delirium has been well-known for quite some time. This applies particularly to the "central anti-cholinergic syndrome" (9), however also to delirium, which does not arise in direct connection to treatments with directly anti-cholinergically working medicaments. The application of the prototypical cholinesterase inhibitor physostigmine is exemplarily mentioned with relevant complications not found with narcotically working acute sedatives (10).

The favourable experiences made thereby were transferred also to the POD. In 1978, in the literature, there were already recommendations for the avoidance of delirious conditions after completion of the anesthesia, by using the injection of a single dose physostigmine while under still the influence of the anesthetic (11). The therapy of an existing case, in particular one manifesting after a lucid post-operative period, does not address delirium itself however, so that this application must be rated as intraoperative prophylaxis of a substance-induced (directly with effects in connection with the anesthetic) delirium.

WO 00/032185 A reveals the effects on the cholinergic system to the therapy of delirium, and also under it the PODs, which is now called "cholinergic delirium". In WO 00/032185 A, delirium is understood to develop within the succeeding 48 to 72 hours without a treatment or an infusion with substances which block the cholinergic system. WO 00/032185 A discloses the use of cholinesterase inhibitors for treating the PODs after an operation. Concrete examples of the use of galanthamine and its

derivatives for treating PODs is disclosed in WO 00/32185 A. The
WO 00/32185 A publication contains as the only example the case of
a female patient, who had suffered a lithium intoxication and
whose occurring delirium was successfully treated with the
5 cholinesterase inhibitor "rivastigmine", an irreversible inhibitor
of the cholinesterases, which has its effect by covalent
modification (carbamylation) in the course of the medicamentous
therapy through many years of existing bipolar disturbance of
these enzymes. The invention is concerned with medicament-induced
10 delirium.

At present there are no suitable or accepted medicaments for
the indication of POD as well as no published systematic clinical
studies which support the specific effectiveness of a medicament
with strict scientifically defined POD. Thus, there still exists a
15 substantial medical need for a pharmacological means for treating
fast occurring POD which terminates quickly. Special value must
be put on minimum side effects of such a therapy, since a POD
patient is by definition in the post-operative recovery phase and
therefore exhibits reduced tolerance to physiological and
20 psychological stress.

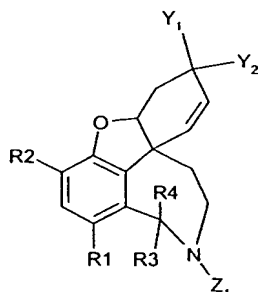
The invention is the basis to meet this need.

The use of galanthamine and galanthamine derivatives having
cholinergic activity are the subject according to invention and
their use for manufacturing medicaments for the treatment of post-
25 operative delirium and/or subsyndromes of post-operative delirium.

Further the use of galanthamine and galanthamine derivatives
having cholinergic activity are suggested according to the
invention for manufacturing medicaments for the preventive
treatment of post-operative delirium and/or subsyndromes of post-
30 operative delirium.

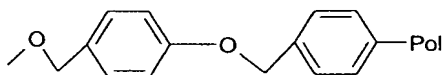
Preferably the galanthamine derivatives have the general

formula Ia



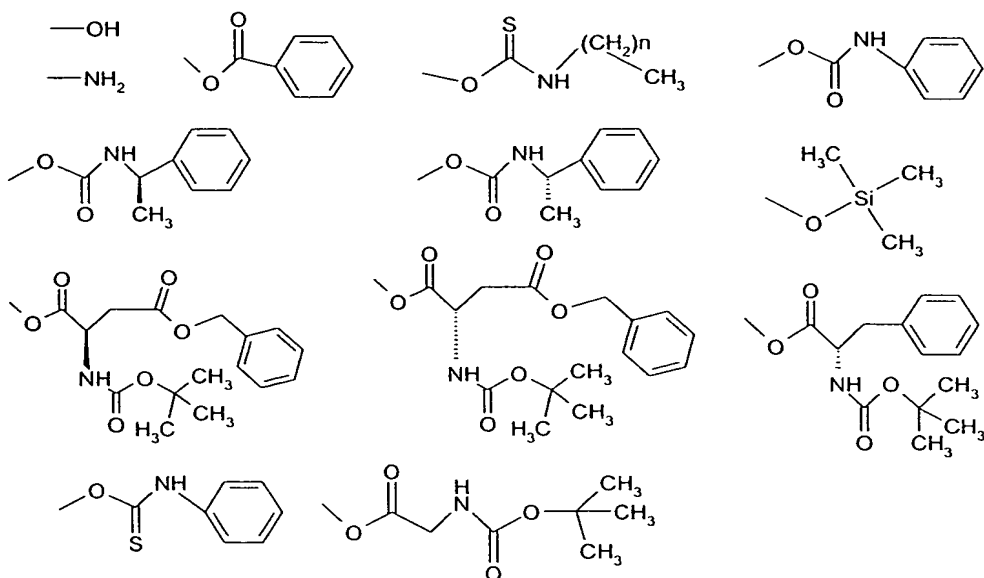
Ia

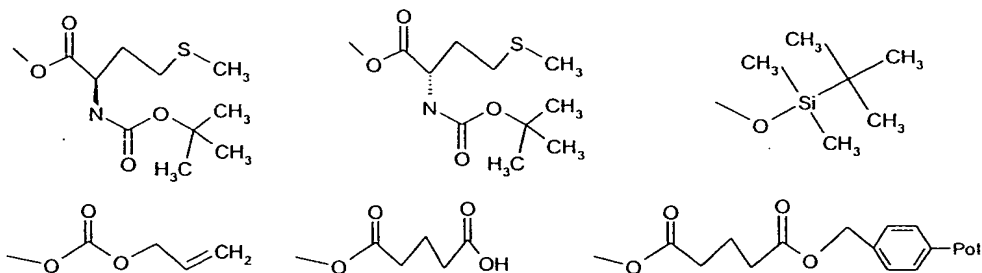
and the salts thereof, wherein R_1 is H, branched or straight chain
 5 (C₁-C₆) alkyl, Br, NO₂, NR₅R₆ wherein R₅ and R₆ are the same or
 different and are selected from H, branched or straight chain (C₁-
 C₆) alkyl, and wherein R₂ is OH, branched or straight chain (C₁-C₆)
 alkyl, methoxy, phenoxy or the following group



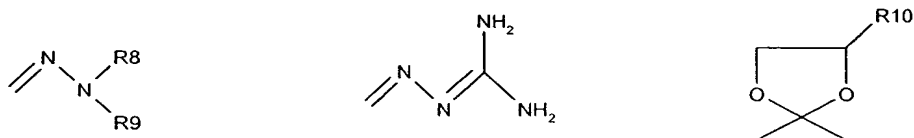
10

whereby Pol is a polymer, preferably one in accordance with WO-
 01/174820A1, and wherein R₃ and R₄ either at the same time or
 alternatively are H, D, CN, straight chain or branched (C₁-C₆)
 15 alkyl or a carbonyl group together, wherein Y₁ and Y₂ alternatively
 are H or a group selected from:



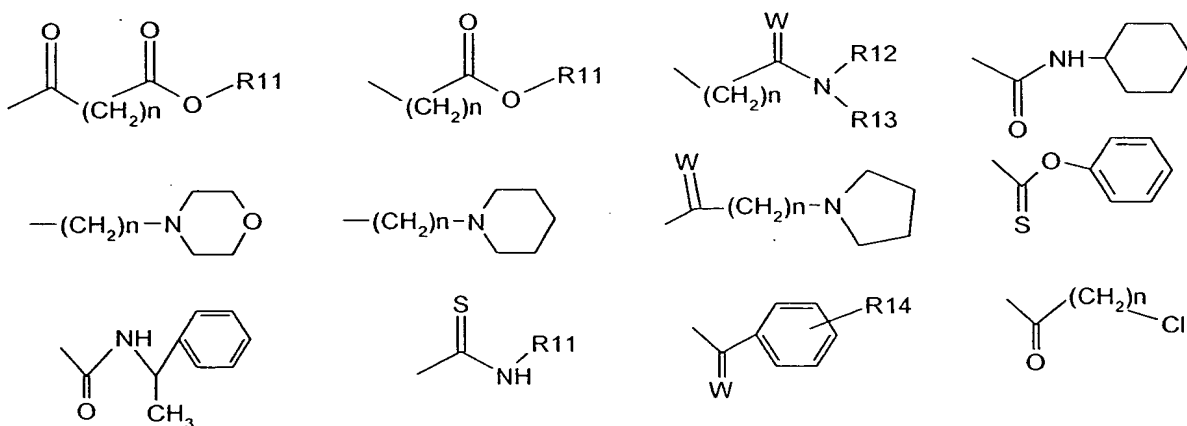


wherein n represents a value of 0, 1 to 15, and Pol has the
 5 meaning indicated above, and wherein Y_1 and Y_2 further represent
 together a carbonyl group ($=O$), $=NH$, $=N-OR_7$, wherein R_7 is H,
 tosylate or branched or straight chain (C_1-C_6) alkyl, or Y_1 and Y_2
 together is a group selected from:

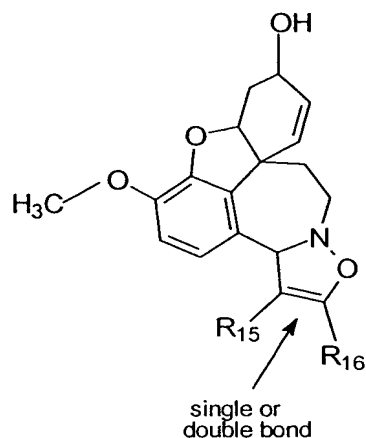


10

wherein R_8 and R_9 are the same or different and are H, branched or
 straight chain (C_1-C_6) alkyl, $-(CH_2)_2-OH$, CHO , $CONH_2$, tBOC (tert-
 Butoxycarbonyl), or mean $-COCOOH$, R_{10} is H or CH_3 , and wherein when
 15 Y_1 is $-O-(CH_2)_2-OH$, Y_2 is OH , and wherein Z_1 is H, branched or
 straight chain (C_1-C_6) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, tri-
 fluoroacetyl, formyl, phenyl or a group selected from:

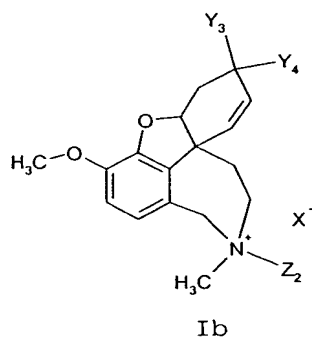


phenyl, chlorophenyl, (trifluoromethyl)-phenyl or 1-naphtyl, wherein R_{14} is H, F, CH_3 , NO_2 , Cl, Br, J, CF_3 , η has the meaning indicated above, m is 0 or 1, and W has the meaning H or O, and
 5 wherein further Z_1 and R_3 form a common ring



wherein R_{15} and R_{16} alternatively mean H, $COOCH_3$, $COOCH_2CH_3$, CN, $COCH_3$.
 10

Other preferred galanthamine derivatives have the general formula Ib

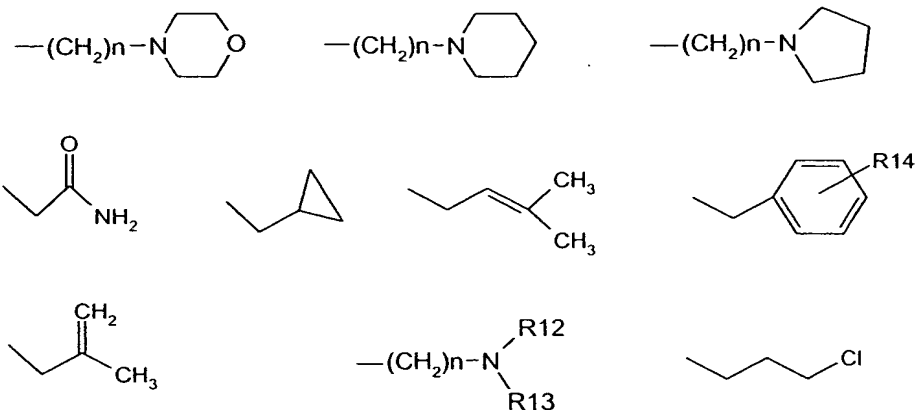


15

wherein Y_3 and Y_4 alternatively mean H and OH, X is Cl, Br or I, Z_2 is oxygen (N-oxide and no counterion), branched or straight chain
 20 (C_1-C_6) alkyl, or (C_2-C_7) alkenyl or (C_2-C_7)

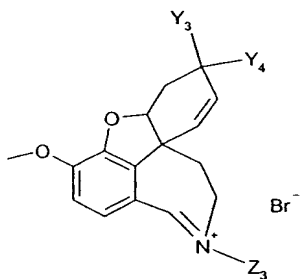
10

alkynyl or a group selected from:



wherein n , R_{12} , R_{13} and R_{14} have the meanings as defined in
 5 accordance with claim 3.

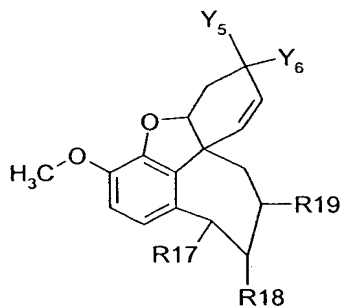
Likewise other useful galanthamine derivatives of the invention that can be used have the general formula Ic



Ic

wherein Y_3 and Y_4 have the meanings defined above, and Z_3 is oxygen (N-oxide and no counterion) or is a methyl group.

Additional galanthamine derivatives used according to invention are further characterized by the general formula Id

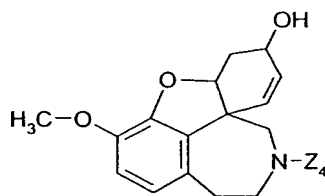


Id

11

and their salts, wherein Y_5 and Y_6 alternatively are H or OH, or together form a keto group, and R_{17} , R_{18} , R_{19} are alternatively for two substituents H, and wherein the third substituent is NH_2 or $CONH_2$.

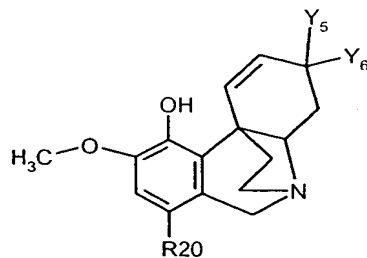
- 5 Further preferable galanthamine derivatives that can be used according to the invention have the general formula Ie



Ie

- 10 or their salts, wherein Z_4 is straight chain or branched (C_1 - C_6) alkyl or 4-bromobenzyl.

Other preferable galanthamine derivatives that can be used according to the invention have the general formula If

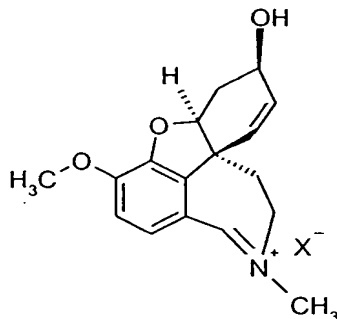


If

15

or their salts, wherein Y_5 and Y_6 have the meanings as defined above, and R_{20} is H or Br.

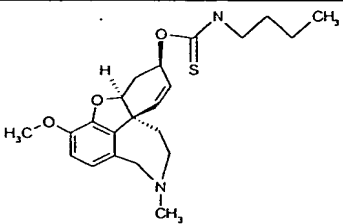
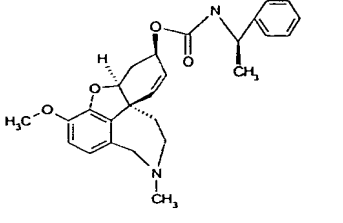
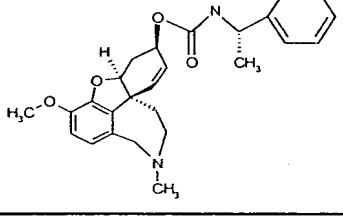
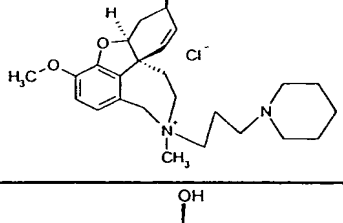
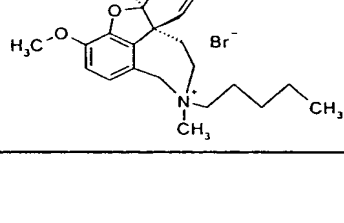
- 20 The use of a galanthamine derivative with the following structural formula is particularly preferred

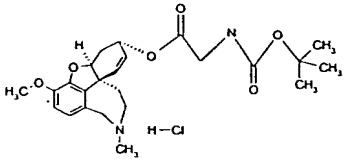
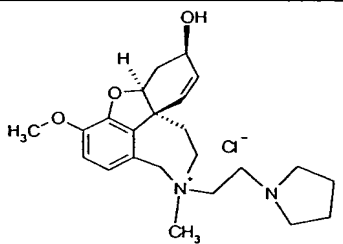
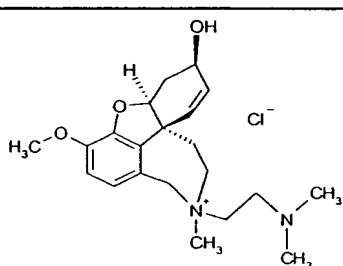
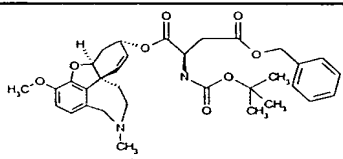
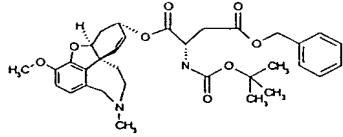


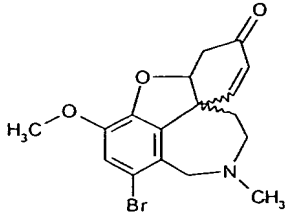
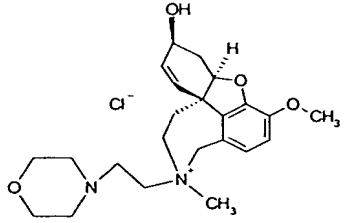
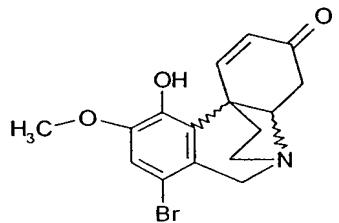
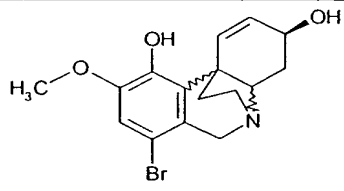
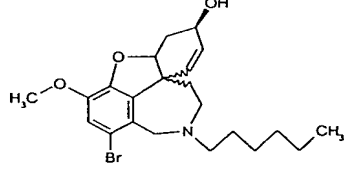
and its pharmaceutical acceptable salts, hydrates or solvates thereof and having the designated chemical name (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-f][2]benzazepinium.

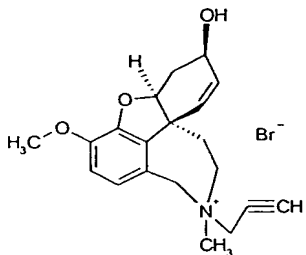
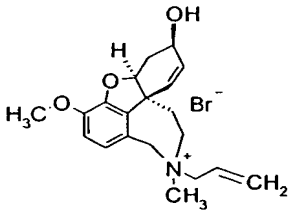
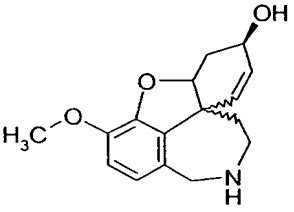
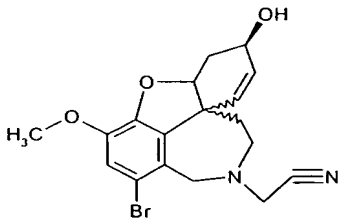
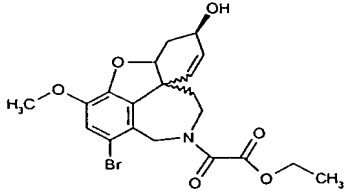
5 The pharmaceutical acceptable salt counterions of (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium are selected from the group of halides, preferably bromide, carboxylic acids with 1-3 carboxyl functions, particularly preferably are tartrate, malonate, 10 fumarate and succinate, and sulfonic acids, preferably methane sulfonic acid.

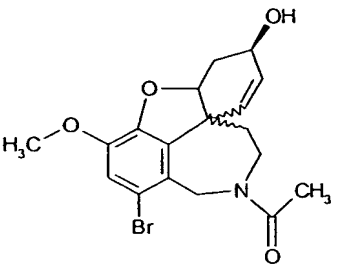
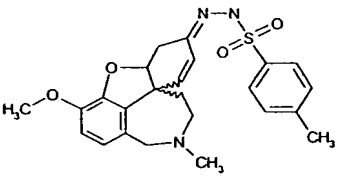
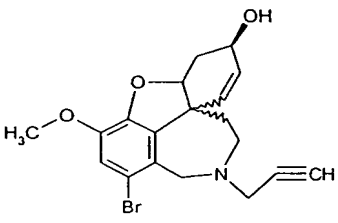
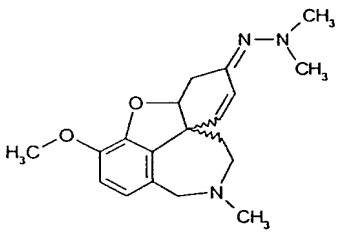
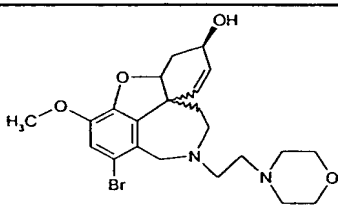
 According to the invention the galanthamine as well as the galanthamine derivatives used in the present invention are prepared by known procedures in the art, like those described in 15 WO 96/12692 A, WO 97/40049 and WO 01/74820. In the present invention the cholinergic activity of galanthamine and its derivatives is substantial, and this characteristic is going to be specified according to the invention using the inhibition of the cholinergic effect of cholinesterases. This characteristic can 20 be shown on the following table - as the concentration values for acetyl and/or butyrylcholinesterase, lowered by 50% inhibition.

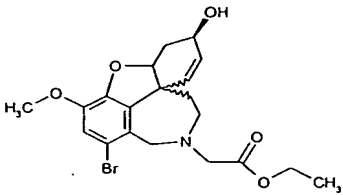
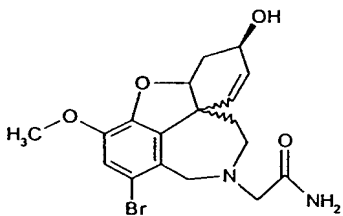
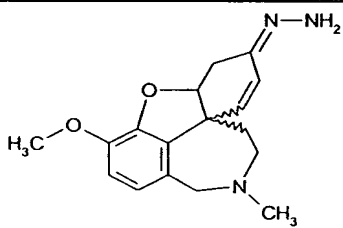
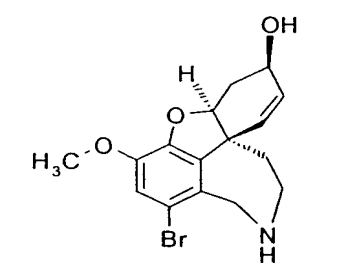
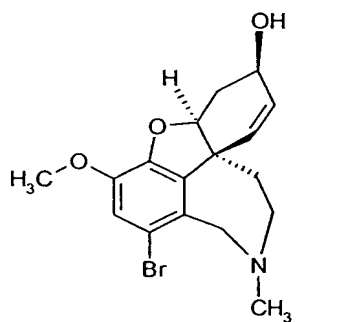
Nr	STRUCTURE	stereo	Acetyl- cholinesterase IC-50 (μM)	Butyryl- cholinesterase IC-50 (μM)
1		(-)	>100	4.8
2		(-)		70
3		(-)		75
4		(-)	6	
5		(-)		

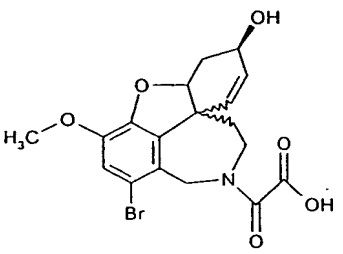
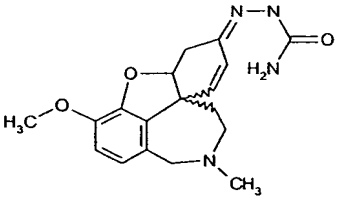
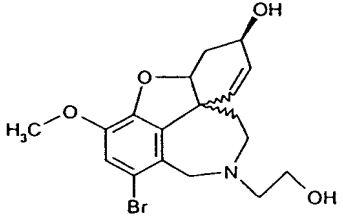
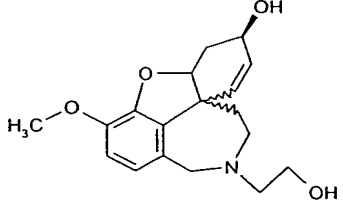
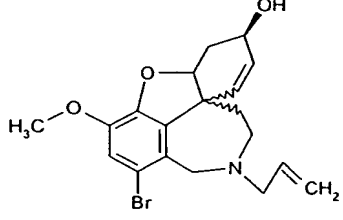
6		(-) epi	45	
7		(-)	2	
8		(-)	8	
9		(-) epi		
10		(-) epi		

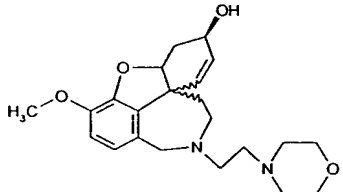
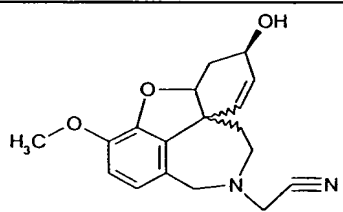
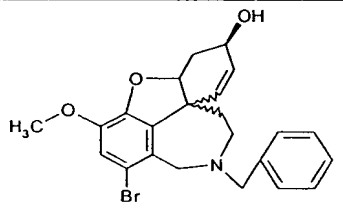
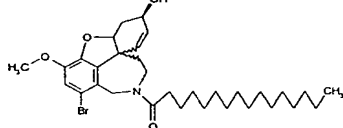
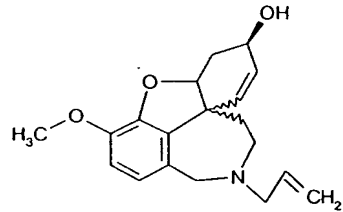
11		(-/+)	50	
12		(+)	57	13
13		(-/+)	5	
14		(-/+)	>100	18
15		(-/+)	40	0.45

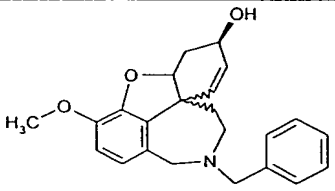
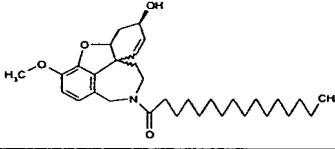
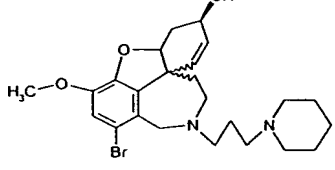
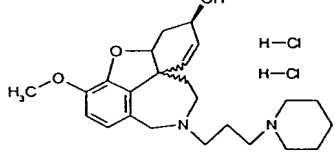
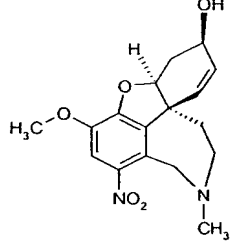
16		(-)	1.4	1.7
17		(-)		
18		(-/+)	7	
19		(-/+)	>100	70
20		(-/+)	32	11

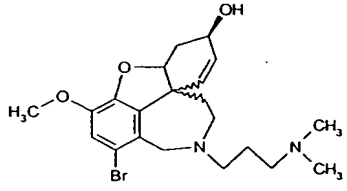
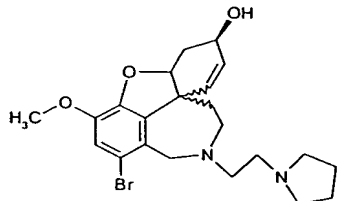
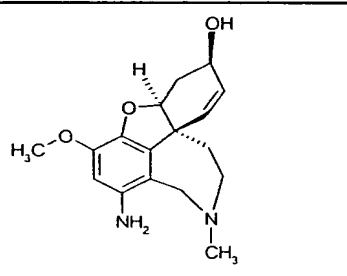
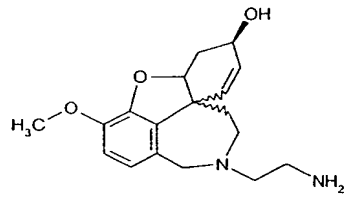
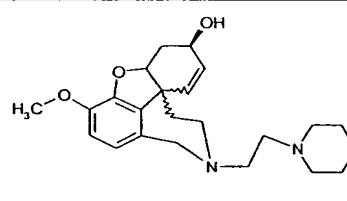
21		(-/+)		
22		(-/+)		
23		(-/+)	63	10
24		(-/+)	80	60
25		(-/+)	3	

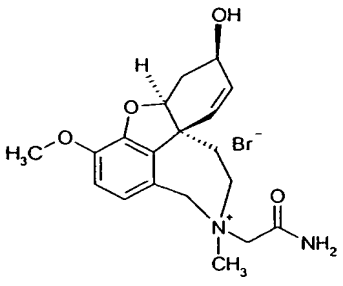
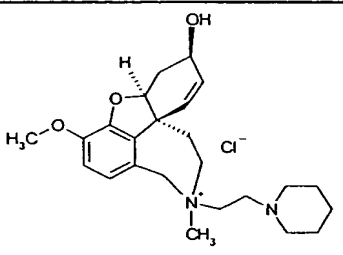
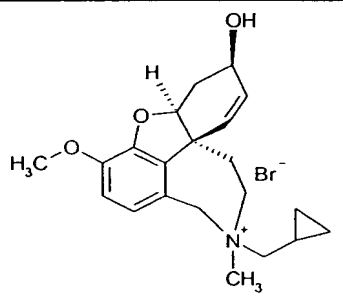
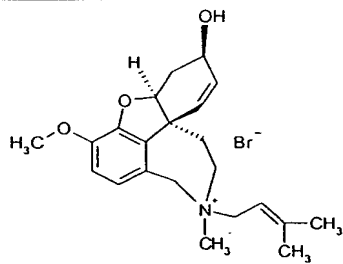
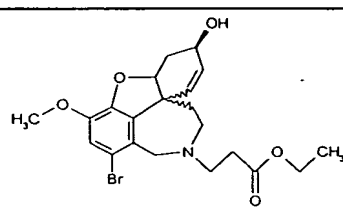
26		(-/+)	20	
27		(-/+)	>100	15
28		(-/+)	40	
29		(-)	3	
30		(-)	4	

31		(-/+)		
32		(-/+)	>100	20
33		(-/+)	34	6.4
34		(-/+)	14	26
35		(-/+)	>100	2.6

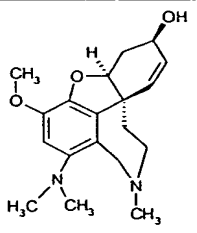
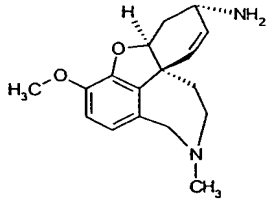
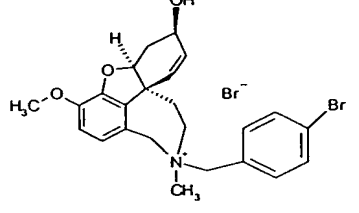
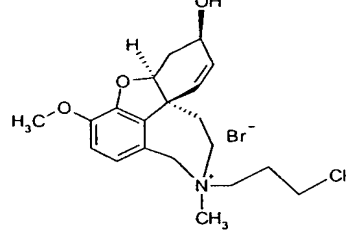
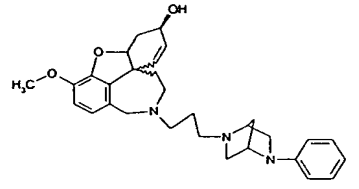
36		(-/+)	13	7
37		(-/+)	30	>100
38		(-/+)	>100	0.24
39		(-/+)		
40		(-/+)	3.3	3.1

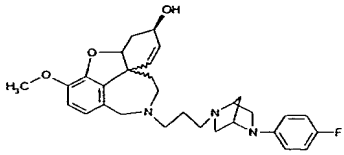
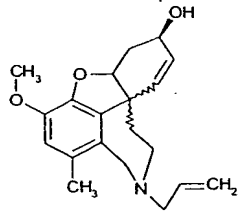
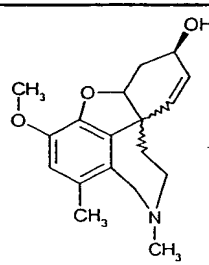
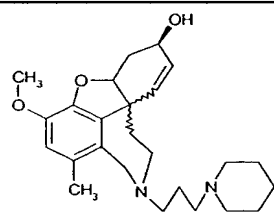
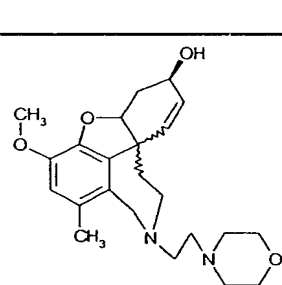
41		(-/+)	0.7	0.65
42		(-/+)		
43		(-/+)	0.2	
44		(-/+)		
45		(-)	>100	25

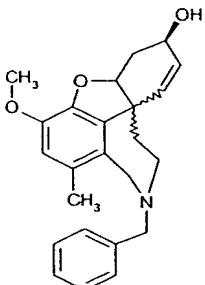
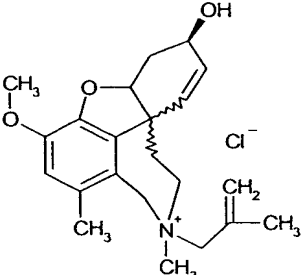
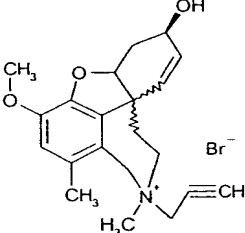
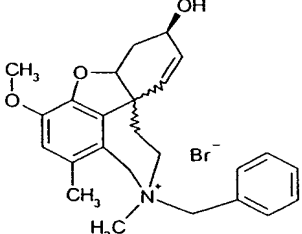
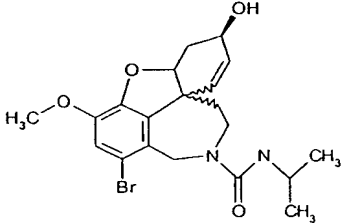
46		(-/+)		
47		(-/+)		
48		(-)	77	4.9
49		(-/+)		
50		(+/-)		

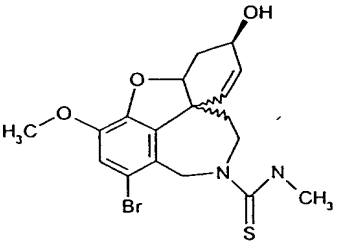
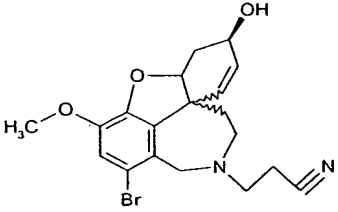
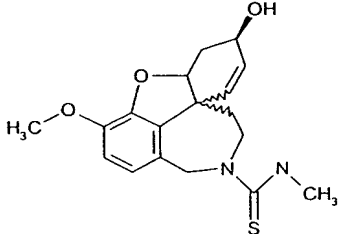
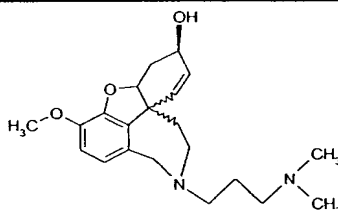
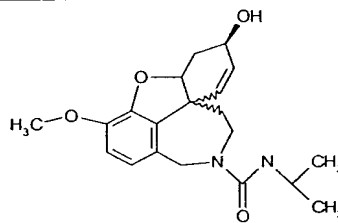
51		(-)	3.1	2.5
52		(-)	4	
53		(-)	1.2	3.6
54		(-)	0.2	0.21
55		(-/+)	>100	19

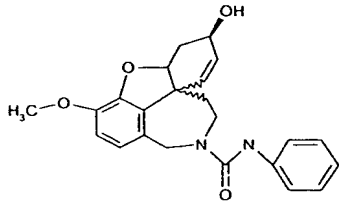
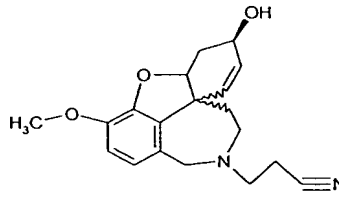
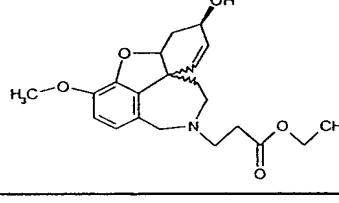
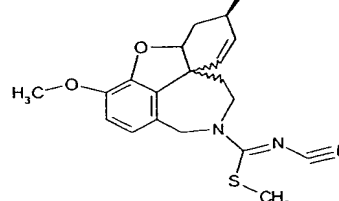
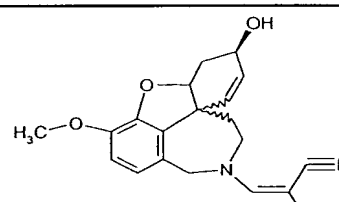
24

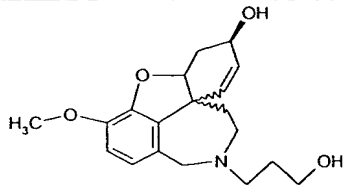
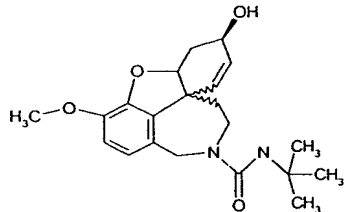
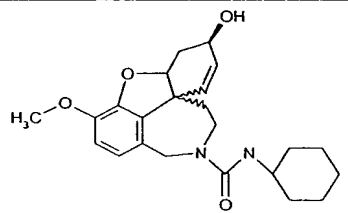
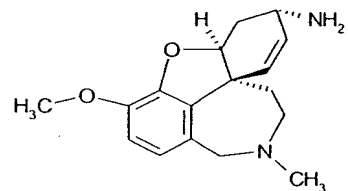
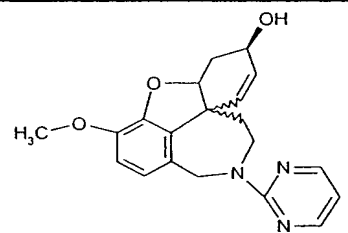
56		(-)	>100	0.47
57		(-) epi		
58		(-)	0.2	0.6
59		(-)	0.35	4.4
60		(-/+)	24	7.5

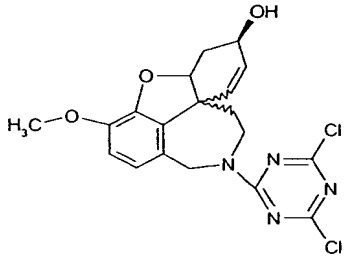
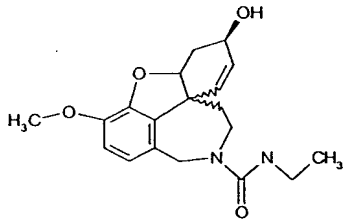
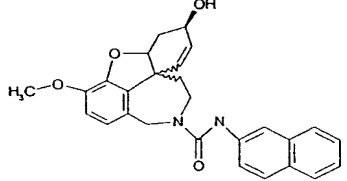
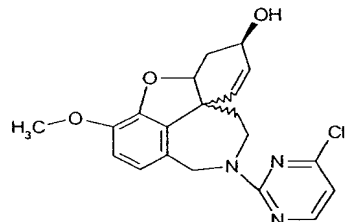
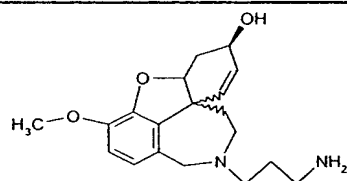
61		(-/+)	5.2	5
62		(-/+)	>100	2.3
63		(-/+)	>100	17
64		(-/+)	46	0.6
65		(-/+)	>100	5.2

66		(-/+)		
67		(-/+)	70	2.4
68		(-/+)	78	2.5
69		(-/+)	47	0.7
70		(-/+)	>100	25

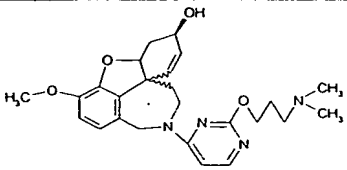
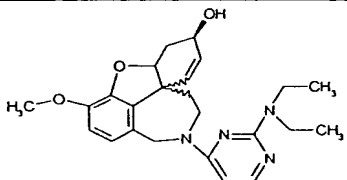
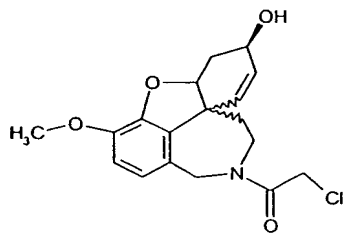
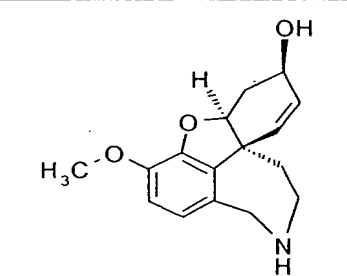
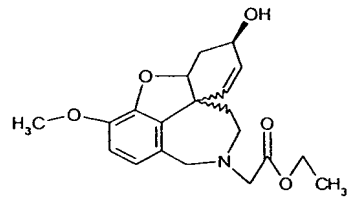
71		(-/+)	31	20
72		(-/+)	>100	43
73		(-/+)	23	30
74		(-/+)	6	10
75		(-/+)	4.2	>100

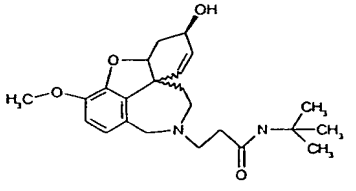
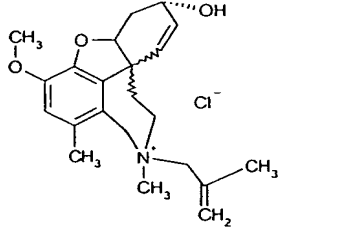
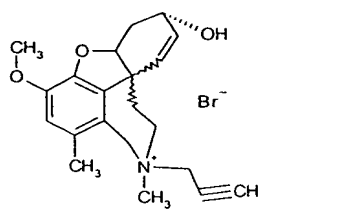
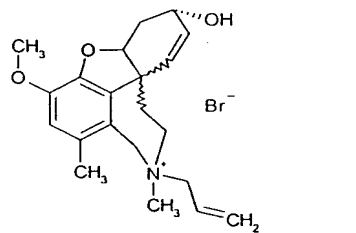
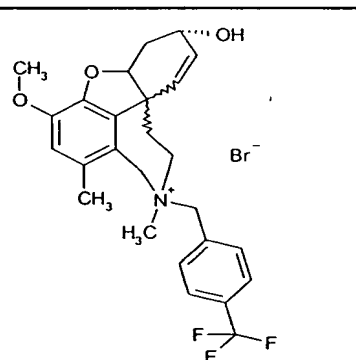
76		(-/+)	70	>100
77		(-/+)	90	>100
78		(-/+)	9.5	17
79		(-/+)	25	0.54
80		(-/+)	28.5	>100

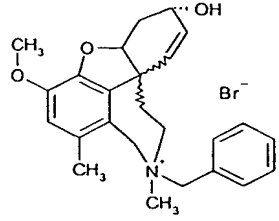
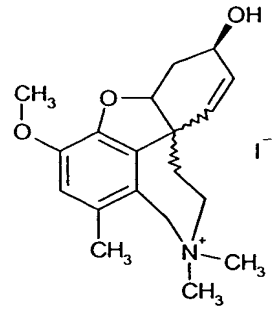
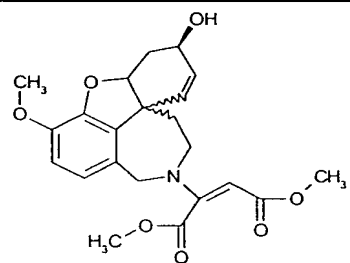
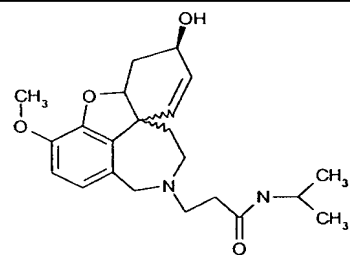
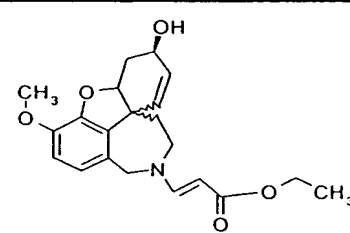
81		(-/+)	7.2	21
82		(-/+)	4.8	>100
83		(-/+)	6.7	>100
84		(-) epi	40	6
85		(-/+)	38	30

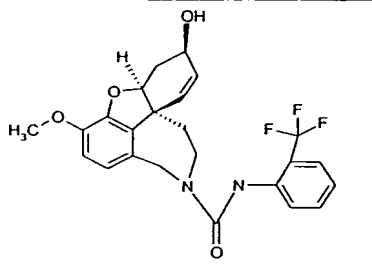
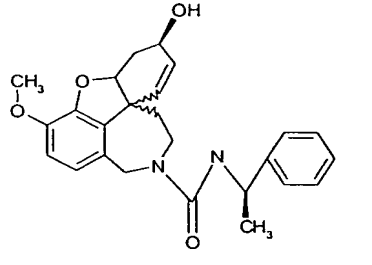
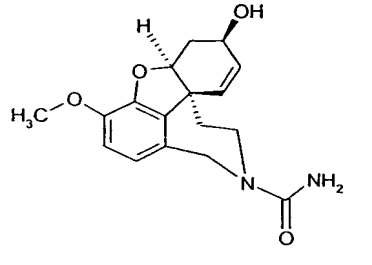
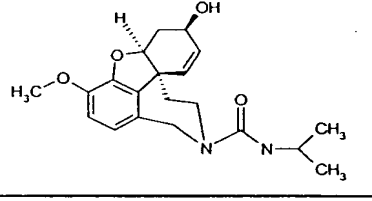
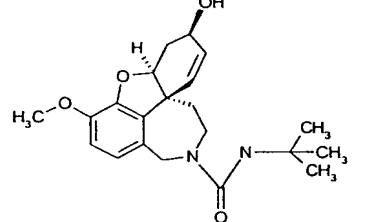
86		(-/+)		
87		(-/+)	33	>100
88		(-/+)	36	>100
89		(-/+)	66	>100
90		(-/+)	3.4	11

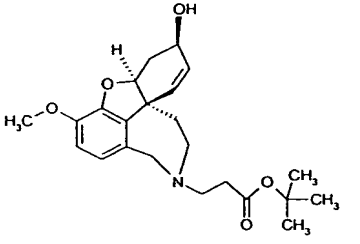
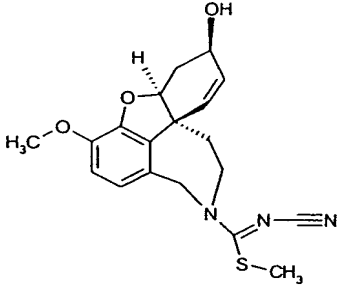
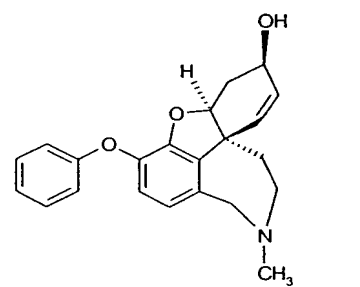
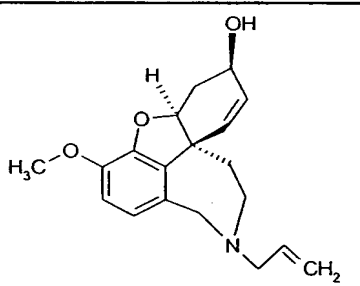
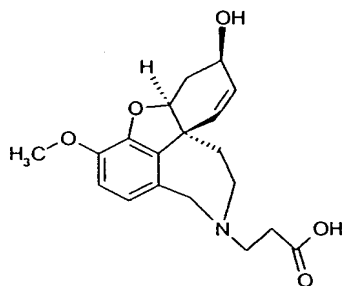
91		(-/+)	21	>100
92		(-/+)	24	>100
93		(-/+)	5	
94		(-/+)	70	40
95		(-/+)	40	>100

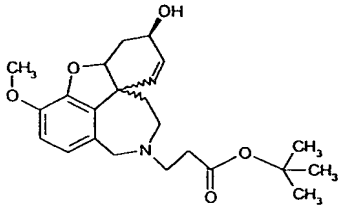
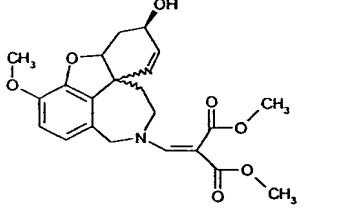
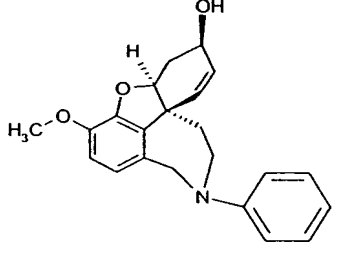
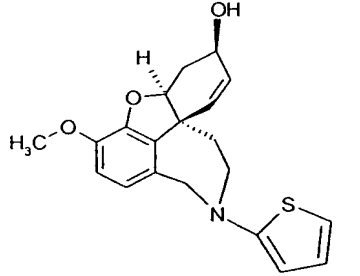
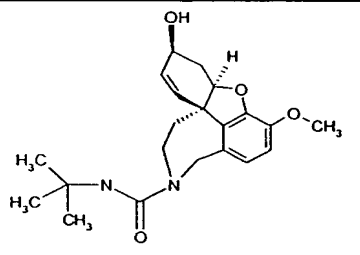
96		(-/+)	7.4	36
97		(-/+)	25	>100
98		(-/+)	17.5	20
99		(-)	2.4	4
100		(-/+)	40	90

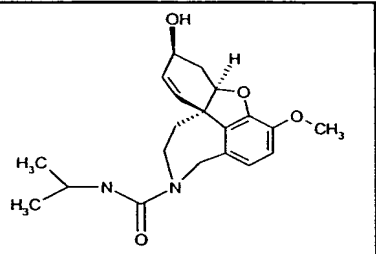
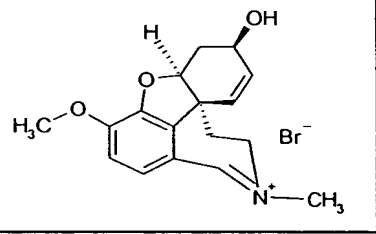
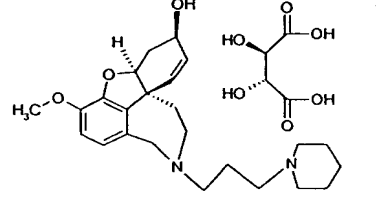
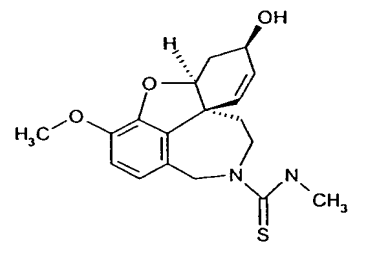
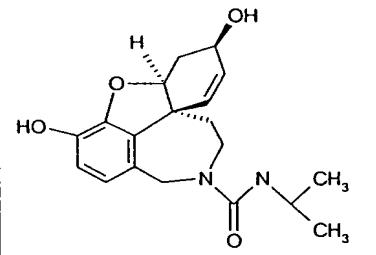
101		(-/+)	45	26
102		(-/+ epi	>100	95
103		(-/+ epi	59	45
104		(-/+ epi	>100	52
105		(-/+ epi	60	5.4

106		(-/+) epi	>100	3
107		(-/+)	>100	14
108		(-/+)	140	80
109		(-/+)	54.5	36
110		(-/+)	50	>100

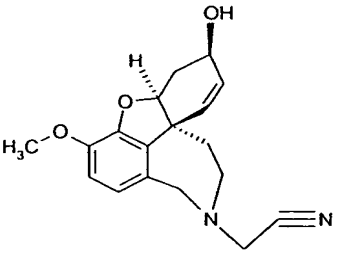
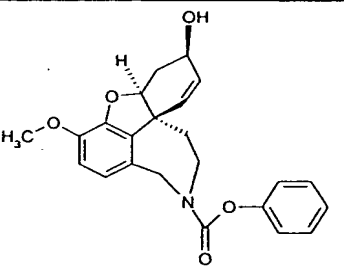
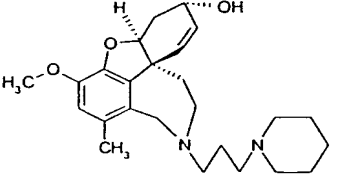
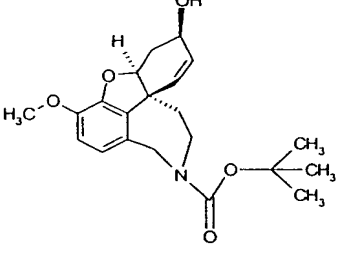
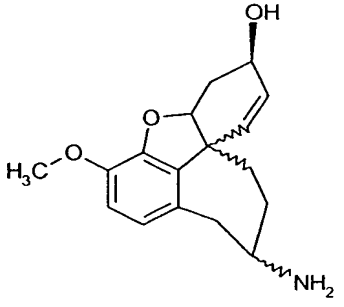
111		(-)	30	>100
112		(-/+)	30	>100
113		(-)	44	>100
114		(-)	2.6	10
115		(-)	2.5	7

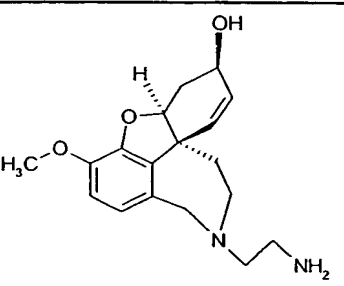
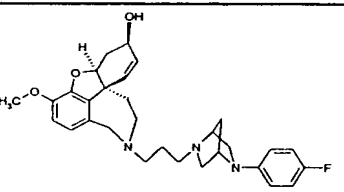
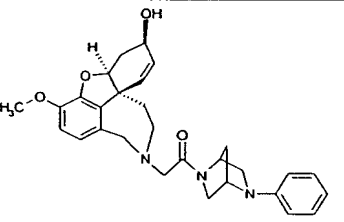
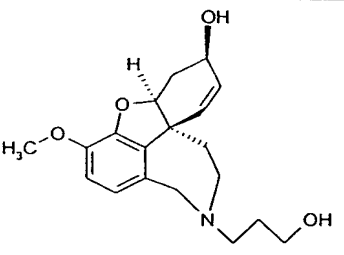
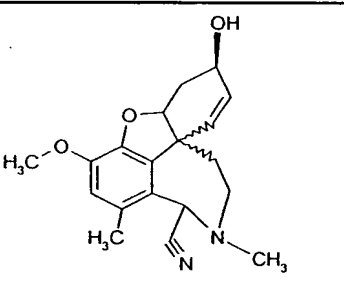
116	 <chem>CC(C)(C)OC(=O)CCN1CC[C@]23C[C@H](O)C=C[C@H]2O[C@H]1C=C[C@@H]3C</chem>	(-)	15	4
117	 <chem>CSC#NCCN1CC[C@]23C[C@H](O)C=C[C@H]2O[C@H]1C=C[C@@H]3C</chem>	(-)	6.7	30
118	 <chem>CN1CC[C@]23C[C@H](O)C=C[C@H]2O[C@H]1C=C[C@@H]3C</chem>	(-)	21	3.4
119	 <chem>C=CCN1CC[C@]23C[C@H](O)C=C[C@H]2O[C@H]1C=C[C@@H]3C</chem>	(-)		
120	 <chem>OC(=O)CCN1CC[C@]23C[C@H](O)C=C[C@H]2O[C@H]1C=C[C@@H]3C</chem>	(-)	42	40

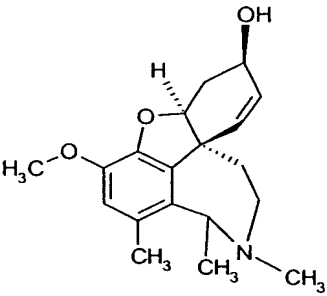
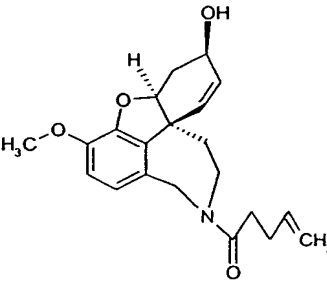
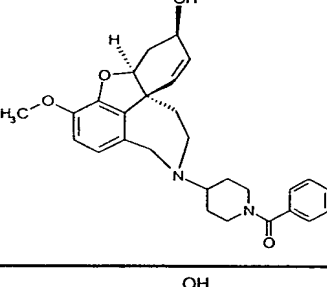
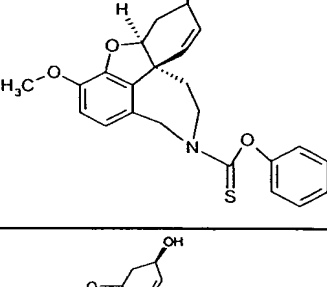
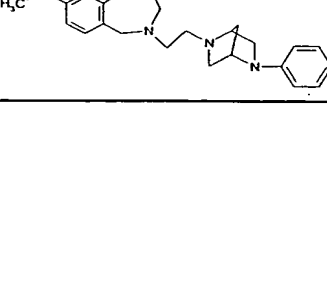
121		(-/+)	33	7.3
122		(-/+)	100	32
123		(-)	0.5	0.24
124		(-)	4	0.54
125		(+)	93	100

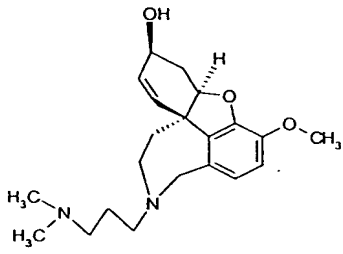
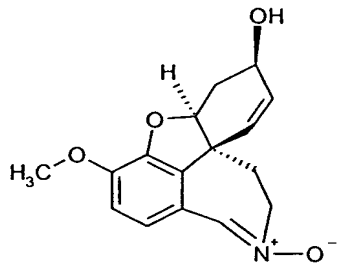
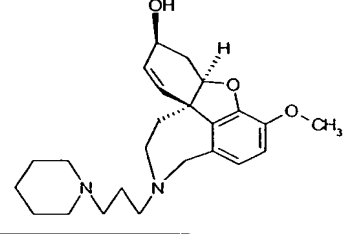
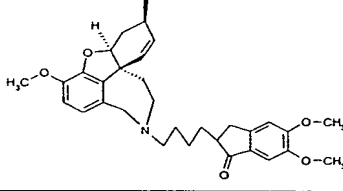
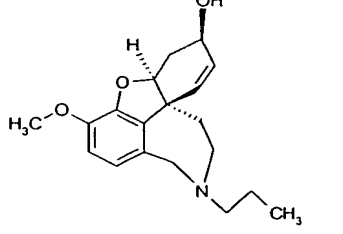
126		(+)	8	90
127		(-)	0.3	1.5
128		(-)	0.3	1.5
129		(-)	18.5	63
130		(-)	6.3	60

131		(-)	0.7	1.2
132		(-)	1.2	100
133		(-)	0.8	>100
134		(-)	40	100
135		(-)	4.2	25

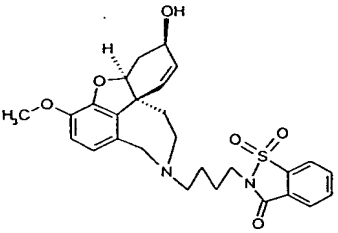
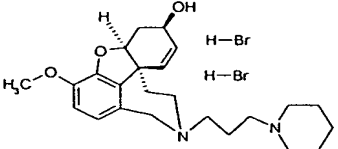
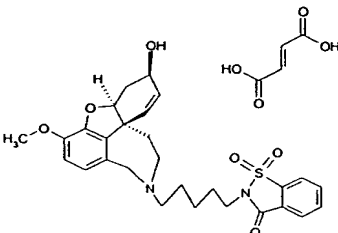
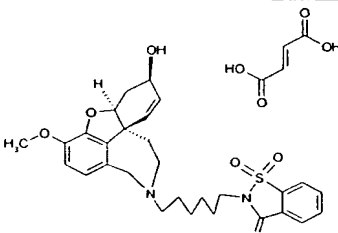
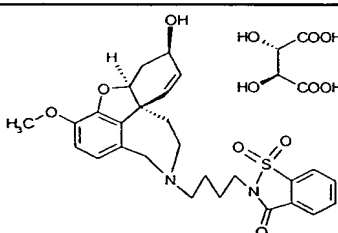
136		(-)	15	32
137		(-)	46	>100
138		(-) epi	>100	70
139		(-)	23	>100
140		(+/-)	5.3	>100

141		(-)	1.3	2.1
142		(-)	3	2.4
143		(-)	8.4	2.4
144		(-)	2.8	5
145		(+/-)	80	>100

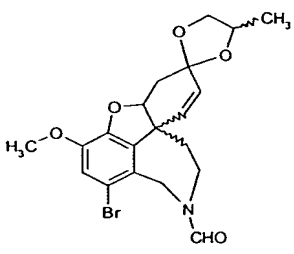
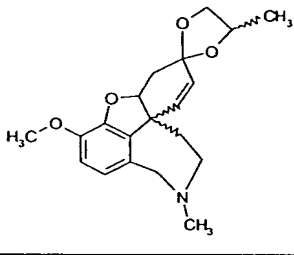
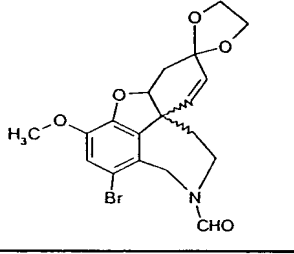
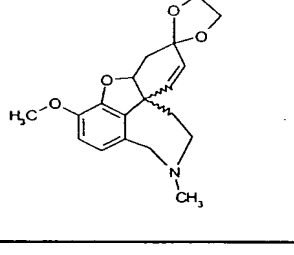
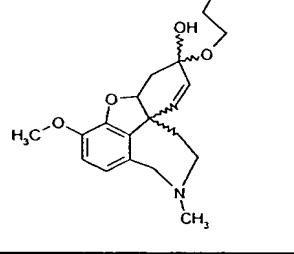
146		(-)	83	30
147		(-)	8.4	2.6
148		(-)	24	3
149		(-)	7.2	>100
150		(-)	2.9	0.85

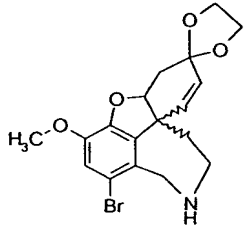
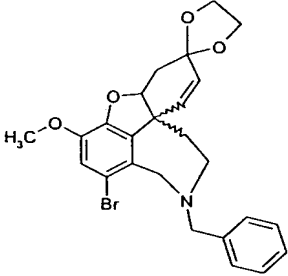
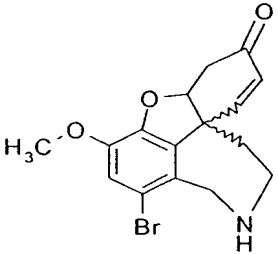
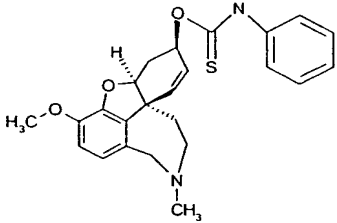
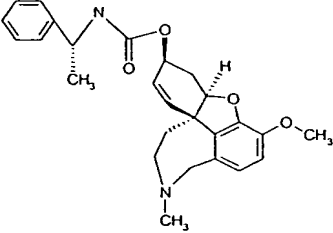
151		(+)	64	67
152		(-)	50	>100
153		(+)	9	23
154		(-)	0.02	0.8
155		(-)	0.3	1.5

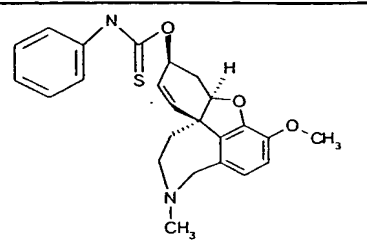
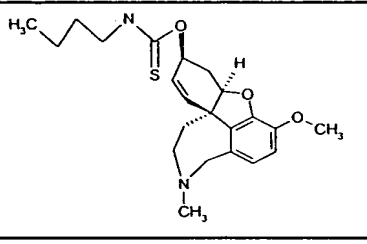
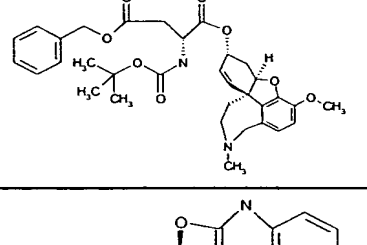
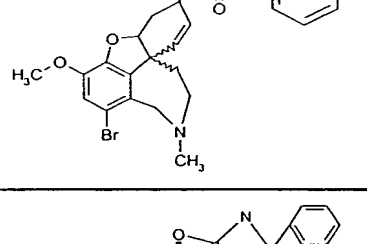
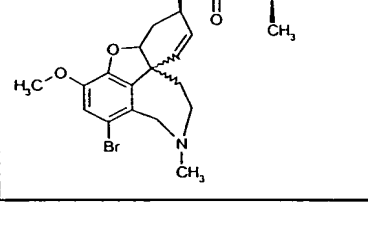
156		(-)	32	30
157		(-)	0.022	0.8
158		(-)	0.0052	0.24
159		(-)	3	>100
160		(-)	3.6	20

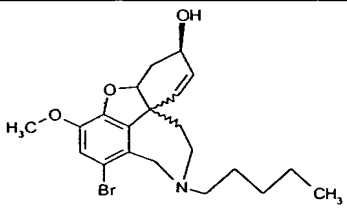
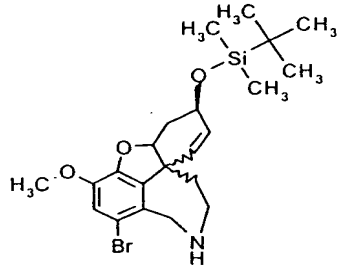
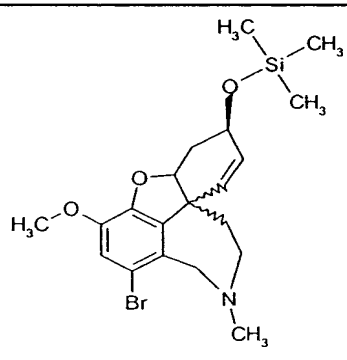
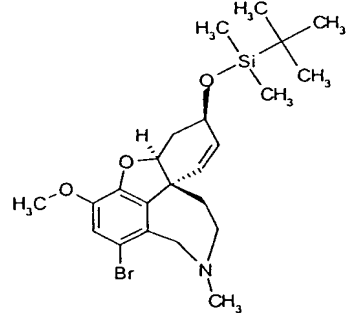
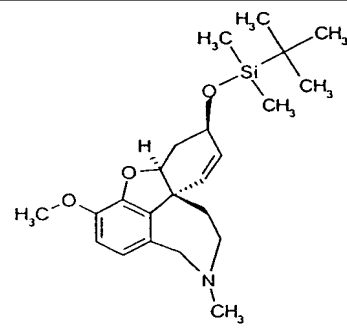
161		(-)	0.022	1.5
162		(-)	0.36	
163		(-)	0.022	
164		(-)	0.043	
165		(-)	0.027	

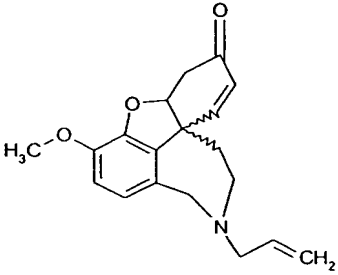
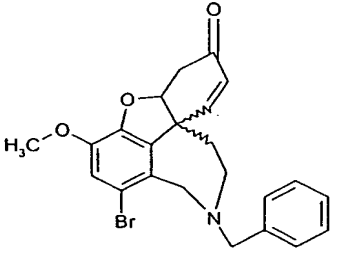
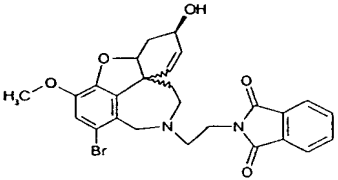
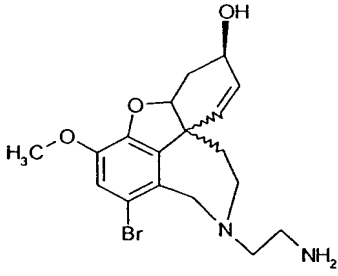
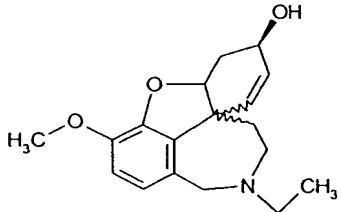
166		(-)	0.023	
167		(-)	0.02	
168		(-)	0.024	
169		(+/-)		
170		(+/-) epi		

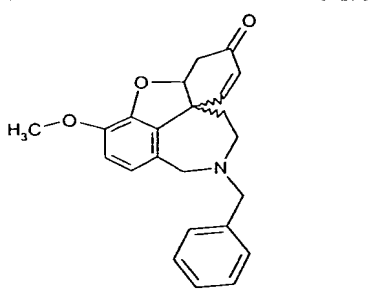
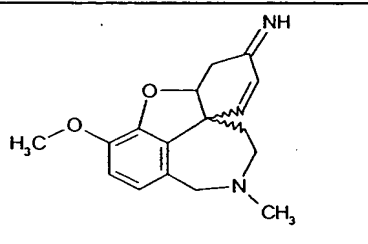
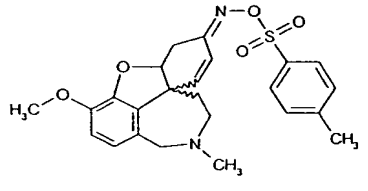
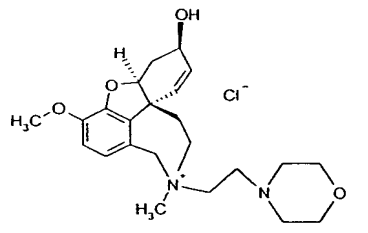
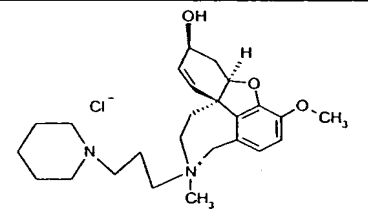
171		(+/-)		
172		(+/-)		
173				
174		(+/-)		
175		(+/-)		

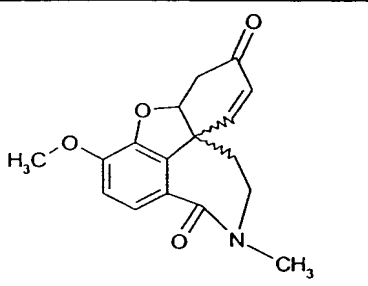
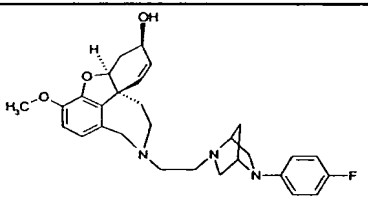
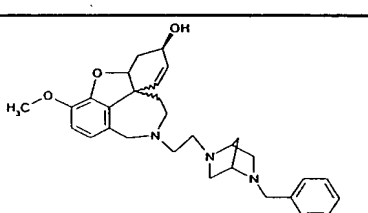
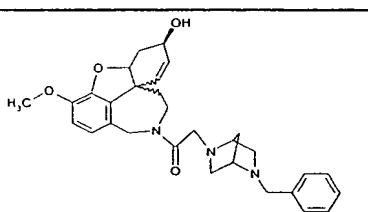
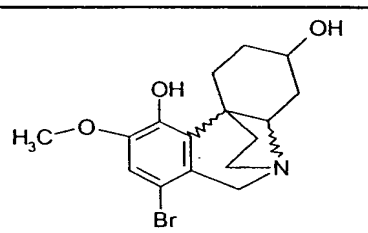
176		(+/-)		
177		(+/-)		
178		(+/-)		
179		(-)	51	30
180		(+)	85	

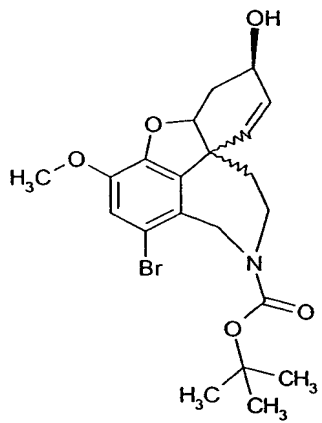
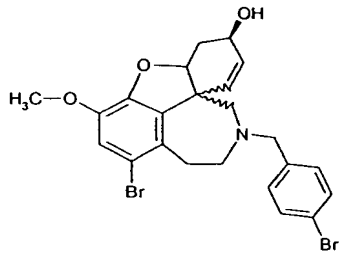
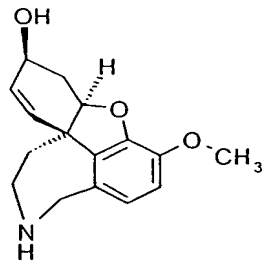
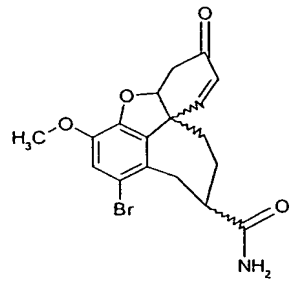
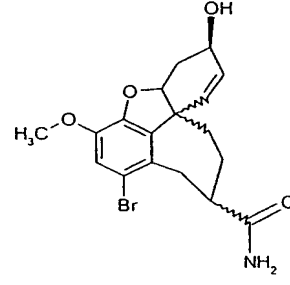
181		(+)	35	
182		(+)	85	
183		(+) epi		
184		(+/-)		
185		(+/-)		

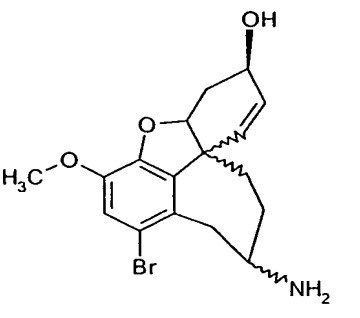
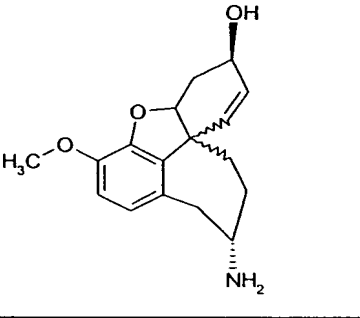
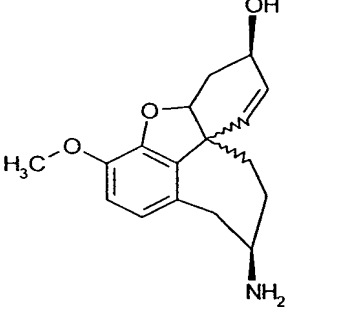
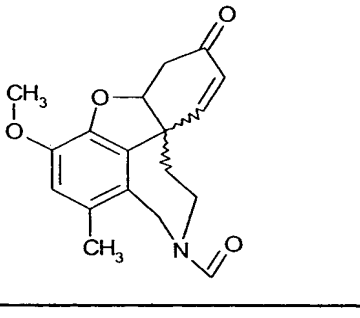
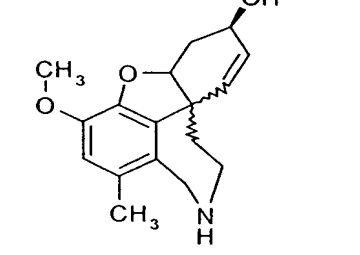
186		(+/-)		
187		(+/-)		
188		(+/-)		
189		(-)		
190		(-)		

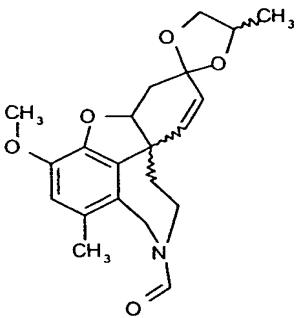
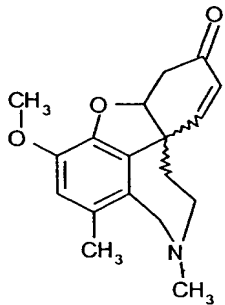
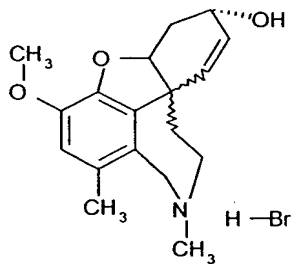
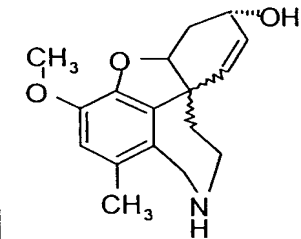
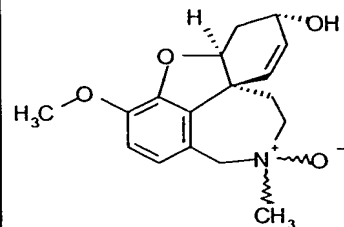
191		(+/-)		
192		(+/-)		
193		(+/-)		
194		(+/-)		
195		(+/-)		

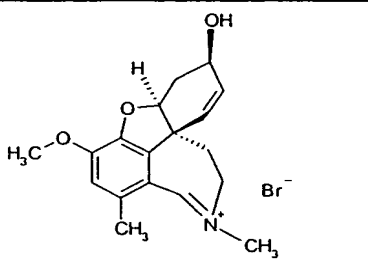
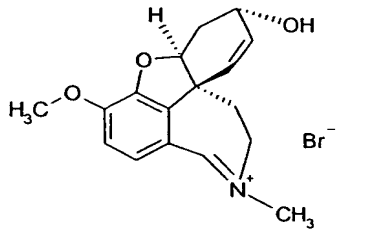
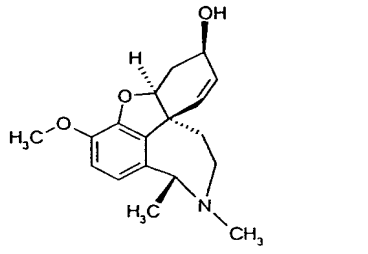
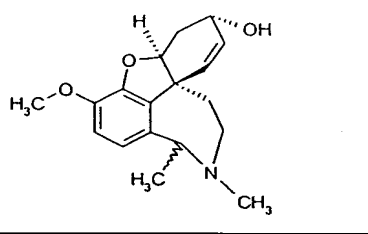
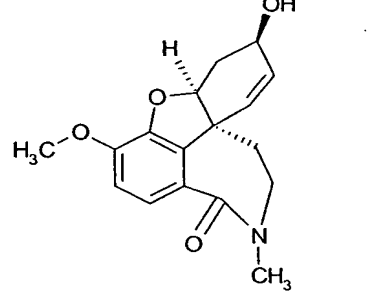
196		(+/-)		
197		(+/-)		
198		(+/-)		
199		(-)	5	
200		(+)		

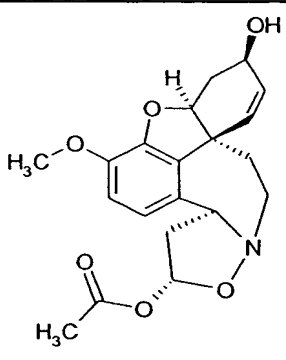
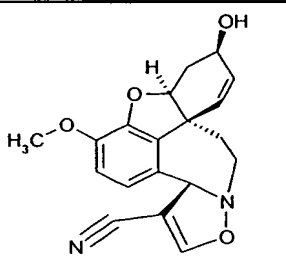
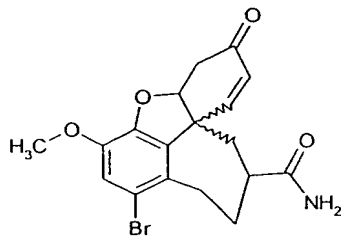
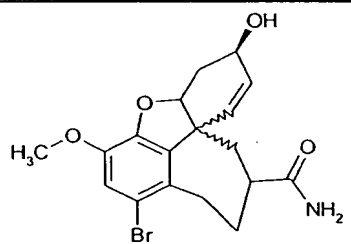
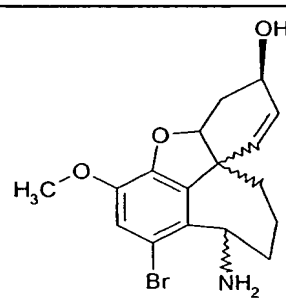
201		(+/-)		
202		(-)		
203		(+/-)		
204		(+/-)		
205		(+/-)	50	

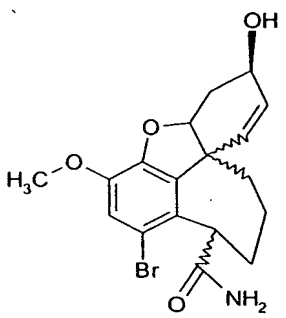
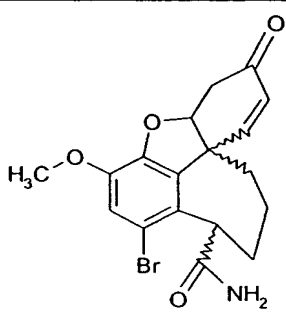
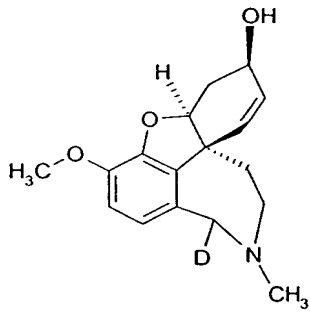
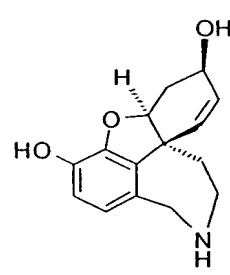
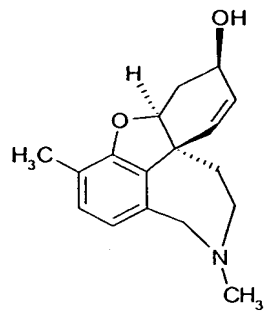
206		(+/-)		
207		(+/-)		
208		(+)		
209		(+/-)		
210		(+/-)		

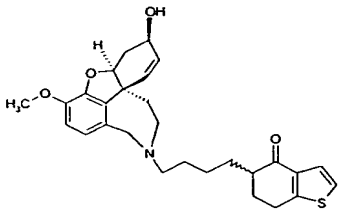
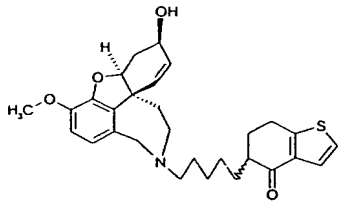
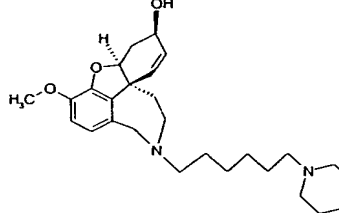
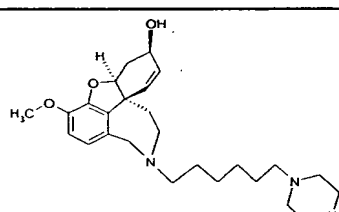
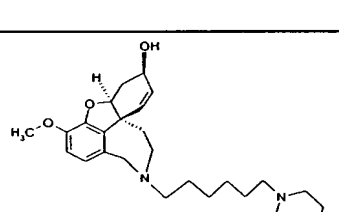
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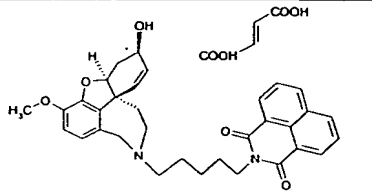
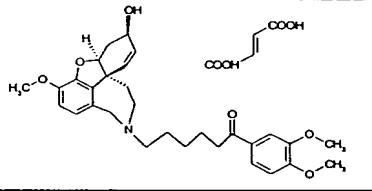
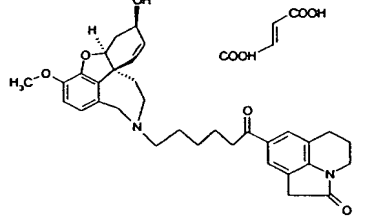
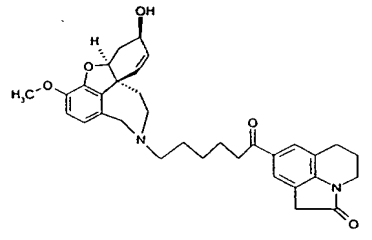
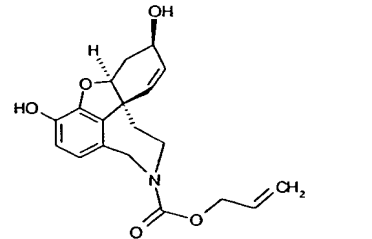
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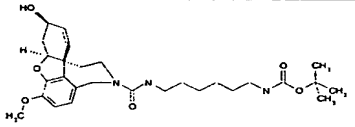
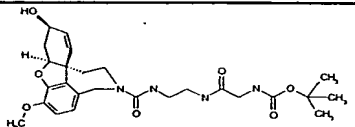
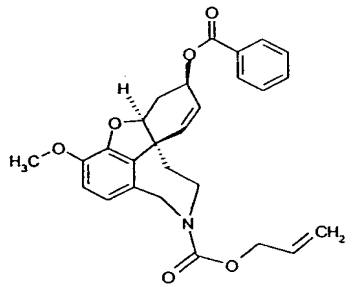
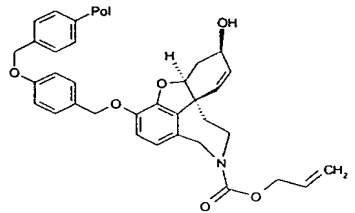
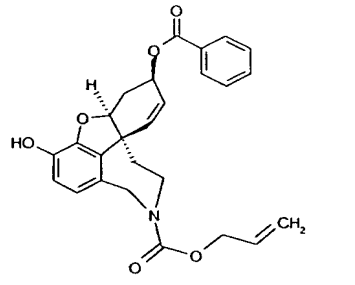
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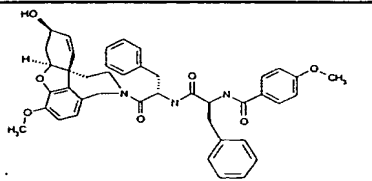
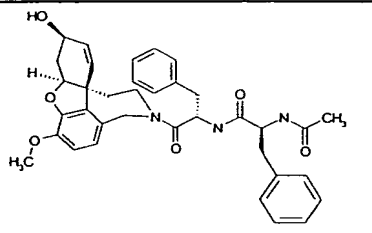
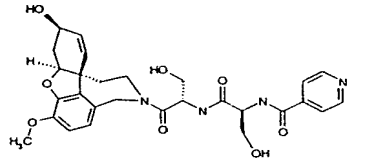
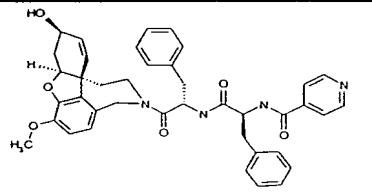
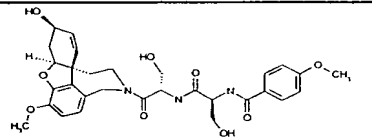
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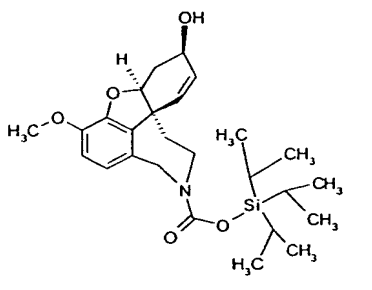
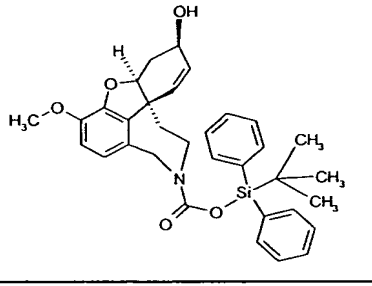
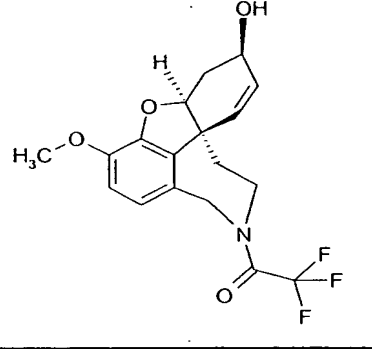
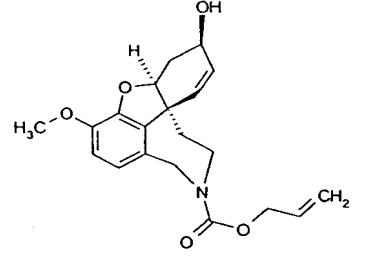
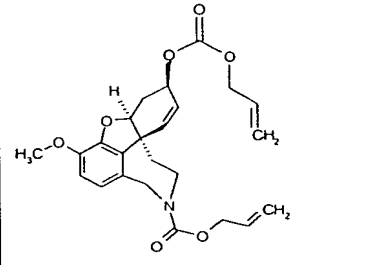
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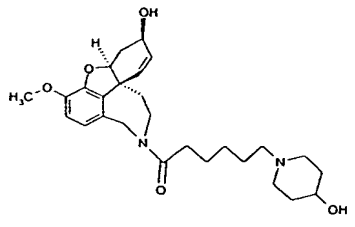
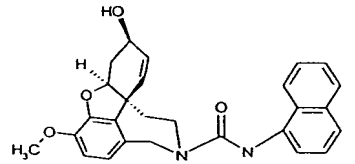
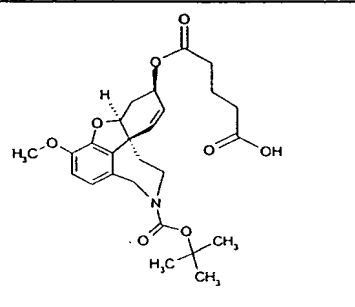
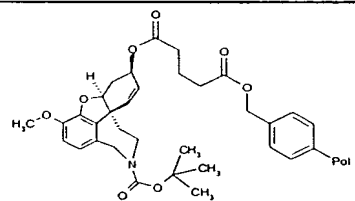
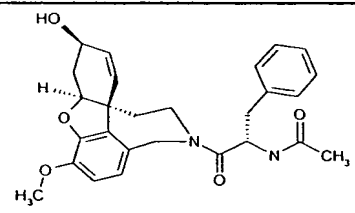
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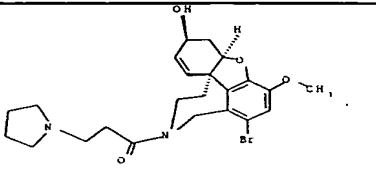
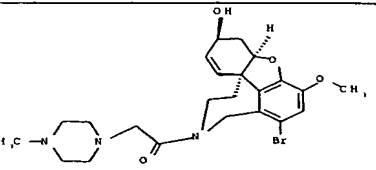
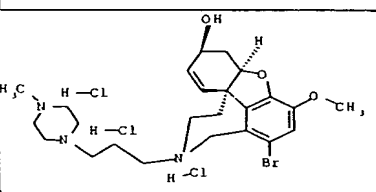
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256		(-)		
257		(-)		
258		(-)		
259		(-)		
260		(-)		

261		(-)		
262		(-)		
263		(-)		
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265		(-)		

266		(-)		
267		(-)	70	>100
268		(-)		
269		(-)		
270		(-)		

271		(+)	>100	66
272		(+)	89	> 100
273		(+)	> 100	31

According to the measured values shown in the table, there is proof for the cholinergic activity of the compounds of the invention, more precisely for the characteristic inhibition of the cholinergic effect of cholinesterases has been provided and therefore these chemical compounds are used to manufacture medicaments for the treatment as well as for the preventive treatment of post-operative delirium and/or subsyndromes of post-operative delirium.

The galanthamine and its derivatives are used as medicaments containing the active substances or a combination of active substances can also be used. Combinations of the invention are also intended to include combinations with other pharmaceutical active substances.

It has now been determined and confirmed by an extensive clinical study that oral administration of galanthamine (as the hydrobromide under the label name of the Reminyl® and used commercially for the therapy of light to moderately severe Alzheimer's illness) to preoperative patients with limited cognitive ability with acute POD, there was an unexpected and large improvement of the symptoms. As particularly surprising must be the fact that the observed side effects of galanthamine administration were very small, although post-operative patients exhibit a increased cholinergic sensitivity according to the observations.

This is to be described on the basis the following applications examples:

Example 1:

The administration of galanthamine or its pharmaceutically acceptable salts and solvates for the therapy or prophylaxis of post-operative deliriums can take place orally (in the form of tablets, capsules, oral solutions or fast-dissolving tablets), intravenously, rectal (in the form of suppositories) or transdermal (in the form of passive or active skin delivering systems of galanthamine).

A preferred form of administration takes place orally, wherein an exemplary administration pattern consists of 8 mg galanthamine hydrobromide given in the form of the active substance directly in free tablets or drinking solutions for the prophylaxis of post-operative deliriums in the evening after the

surgical intervention. On the following four days following the operation day in the morning and at noon 4 mg each are given, then in the evening 8 mg are given. On the fifth post-operative day in each case 4 mg are given in the morning and at noon and the prophylaxis is then terminated. It is understood that the specialists can adjust these dosages according to the body weight of the patient, the general state, etc.

Galanthamine hydrobromide-containing tablets with direct release of the active substance are suitable according to the invention for this kind of administration, and are approved under the trade name Reminyl® for the therapy of the Alzheimer's illness.

Galanthamine-containing oral solutions, which are suitable according to invention for this kind of administration, are described in WO-0130318, wherein such an oral solution can be made in exemplary way as follows:

Galanthamine HBr	5,124 mg
Methyl 4-hydroxybenzoate	1,8 mg
Propyl 4-hydroxybenzoate	0,2 mg
Sodium Saccharin dihydrate	0,5 mg
Water (pH 4.9 -5.1)	1,0 ml

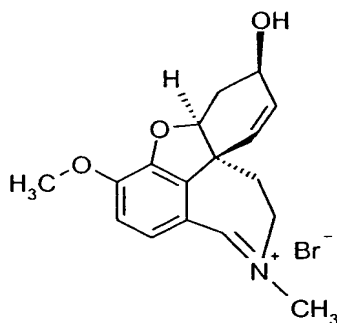
A further oral administration pattern uses capsules with retarded release of the active agent, wherein in the evening after the surgical intervention 8 mg galanthamine hydrobromide are given and on the four days following the surgical procedure at noon or in the evening in each case 8 mg are given too. The capsules usable according to the invention having retarded release of the active agent can be made as described in the document WO 0038686, and the entire teachings of the document are further preferred.

Preferred pharmaceutical forms according to invention are transdermal, and the passive transdermal systems described in WO-9416707 are especially suitable. In this case, a transdermal patch, which releases 10 mg free galanthamine in the span of 24 hours, immediately after waking up from the administration of

anesthetic and on the next four days replaced by a new patch in each case; and on the fifth day no more renewed application takes place.

Of course, combinations of different modes of administration of the active pharmaceuticals described here are possible. In particular, it proves useful to use daily transdermal administration rather than the faster effect oral administration in the evening of the operation such as by providing an oral dose of 4 mg Galanthamine HBr (directly setting free the active from the tablet or oral solution).

Example 2: The administration of (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium took place for example with bromide as the counterion. This example concerns a galanthamine derivative with the following structural formula:



It is however also possible to provide the administration by means of pharmacological acceptable hydrates and solvates. The therapy or prophylaxis of post-operative delirium can take place orally (in the form of tablets, capsules, oral solutions or fast-dissolving tablets), intravenously, rectally (in the form of suppositories) or transdermally (in passive or active form as with the aforementioned skin delivering systems). A preferential form of administration takes place orally, wherein an exemplary administration pattern consists for the prophylaxis of the post-operative delirium that in the evening after the surgical intervention, 2-6 mg of (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide are given as the active substance directly in the form of free tablets or oral solutions. On the four days following the operation day in each case 1-3 mg are then given in the morning and at noon, and in the evening 2-6 mg. On

the fifth post-operative day in each case 1-3 mg are given in the morning and at noon and the prophylaxis is then terminated. It is understood that the specialist can automatically adjust these dosages according to the body weight of the patient, their general state, etc. Likewise in place of bromide, there can be used also
 5 different physiologically acceptable, easily water-soluble salts of the active substance (e.g. different halide, maleate, tartrate).

(4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide
 10 containing tablets having direct release of the active substance, are suitable for administration according to the invention, and they can also be provided with pharmaceutical acceptable coatings. For example:

15

(4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide	2,0 mg
calcium phosphate	25,0 mg
Lactose	5,0 mg
Wheat starch	5,0 mg
Microcrystalline cellulose	40 mg
Talc	2 mg
Magnesium stearate	1,0

The specialist based on the above examples with application experience in usual pharmaceutical practices specified for
 20 galanthamine, can easily make similar pharmaceutical forms for (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a, 5, 9, 10-tetrahydro-6H-benzofuro[3a, 3, 2-ef][2]benzazepinium bromide or similar salts, hydrates or solvates.

In order to be able to test the effect of the pharmaceutical
 25 forms of the invention on patients, a prospective study was accomplished for the prevention of post-operative delirium at five Austrian orthopedic hospitals (two in Vienna, and one each in Linz, Graz and Krems) and all together 229 patients, who underwent

hip replacement and/or combined planned surgical intervention for implantation were part of the study.

Hip/Knee endoprosthesis. The patients of the group were given in the evening following the surgical intervention (day 0) 8 mg galanthamine HCl, then on the days 1 to 4 in each case 4 mg in the morning and at noon and 8 mg in the evening, i.e., 16 mg t.i.d. to the fifth day. The day after the intervention, the dose was reduced to 8 mg b.i.d., starting from that day until the 6th day when no more treatment took place. Patients in the placebo group did not receive distinguishable placebo tablets according to the same pattern.

For the determination of the effectiveness with the help of the "Confusion Assessment Method" (Lit.14) 155 patients could be consulted. In the group of placebos 7 patients (8,5%) developed an post-operative delirium, in the galanthamine group only one patient (1,4%) developed post-operative delirium, which corresponds to a statistically significant difference ($p=0,044$).

The evaluation of the study shows thus in clear way the effectiveness of galanthamine with post-operative delirium.

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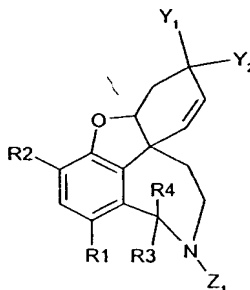
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Patent claims:

1. Use of galanthamine and galanthamine derivatives exhibiting cholinergic activity for manufacturing medicaments for the treatment of post-operative delirium and/or subsyndromes of post-operative delirium.

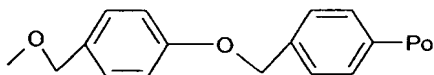
2. Use according to claim 1 for manufacturing medicaments for the preventive treatment of post-operative delirium and/or subsyndromes of post-operative delirium.

3. Use according to claims 1 or 2, characterized by the fact that the galanthamine derivatives have the general formula

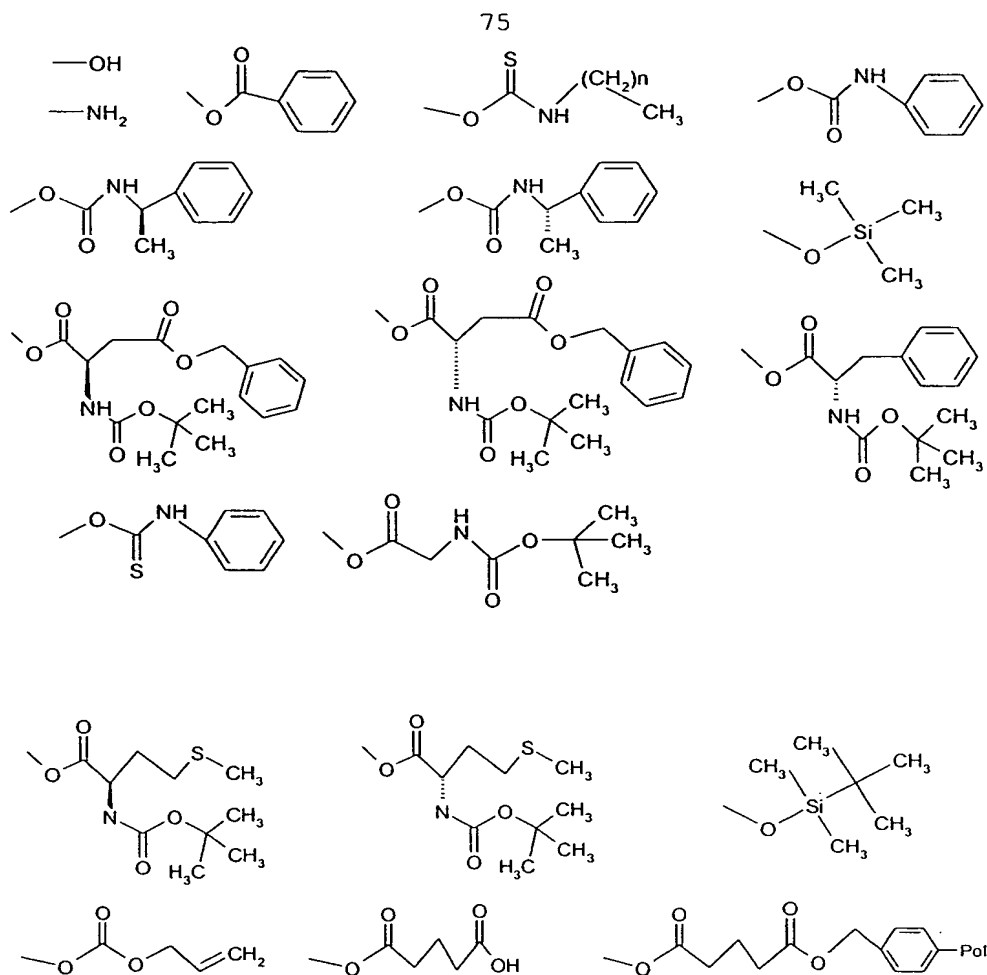


Ia

and the salts thereof, wherein R_1 is H, branched or straight chain (C_1-C_6) alkyl, Br, NO_2 , NR_5R_6 wherein R_5 and R_6 are the same or different and are selected from H, branched or straight chain (C_1-C_6) alkyl, and wherein R_2 is OH, branched or straight chain (C_1-C_6) alkyl, methoxy, phenyloxy or the following group



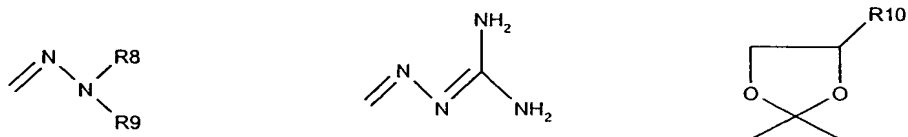
whereby Pol is a polymer, preferably one in accordance with WO-A1-01/174820, and wherein R_3 and R_4 either at the same time or alternatively are H, D, CN, straight chain or branched (C_1-C_6) alkyl or a carbonyl group together, wherein Y_1 and Y_2 alternatively are H or a group selected from:



5

wherein n represents a value of 0, 1 to 15, and Pol has the meaning indicated above, and wherein Y_1 and Y_2 further represent together a carbonyl group ($=O$), $=NH$, $=N-OR_7$, wherein R_7 is H, tosylate or branched or straight chain (C_1-C_6) alkyl, or Y_1 and Y_2 together is a group selected from:

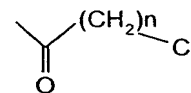
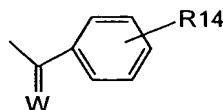
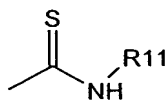
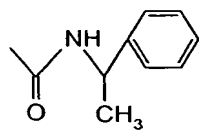
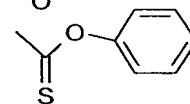
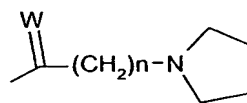
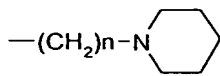
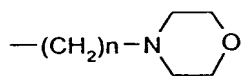
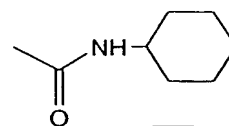
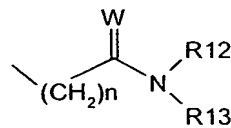
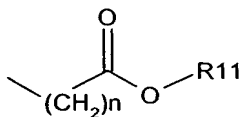
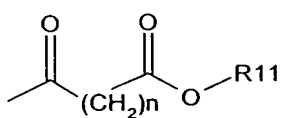
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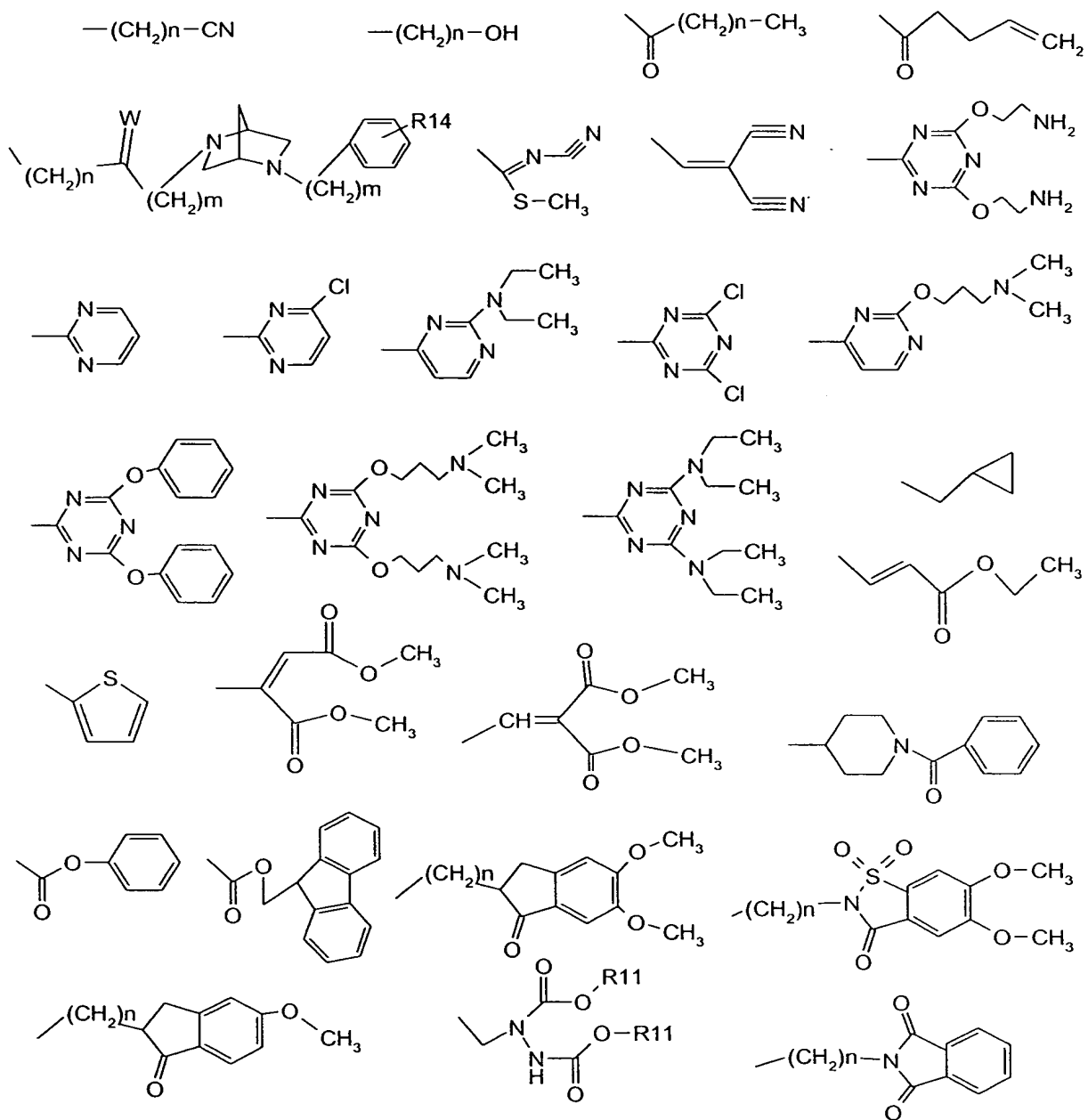


wherein R_8 and R_9 are the same or different and are H, branched or straight chain (C_1-C_6) alkyl, $-(CH_2)_2-OH$, CHO, $CONH_2$, tBOC (tert-Butoxycarbonyl), or mean $-COCOOH$, R_{10} is H or CH_3 , and wherein when Y_1 is $-O-(CH_2)_2-OH$, Y_2 is OH, and wherein Z_1 is H, branched or

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straight chain (C₁-C₆) alkyl, (C₂-C₇) alkenyl, (C₂-C₇) alkynyl, tri-fluoroacetyl, formyl, phenyl or a group selected from:

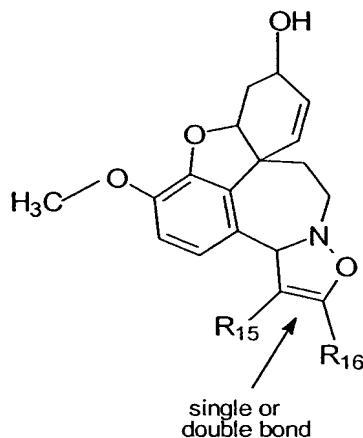




[illegible]

phenyl, chlorophenyl, (trifluoromethyl)-phenyl or 1-naphtyl, wherein R_{14} is H, F, CH_3 , NO_2 , Cl, Br, J, CF_3 , n has the meaning indicated above, m is 0 or 1, and W has the meaning H or O, and wherein further Z_1 and R_3 form a common ring

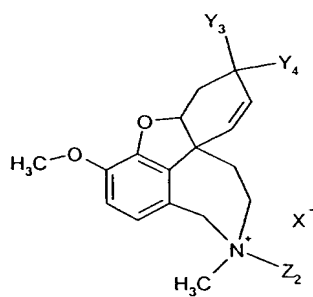
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wherein R_{15} and R_{16} alternatively mean H, $COOCH_3$, $COOCH_2CH_3$, CN, $COCH_3$.

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4. Use according to claims 1 or 2, characterized by the fact that the used Galanthamine derivatives have the general formula Ib

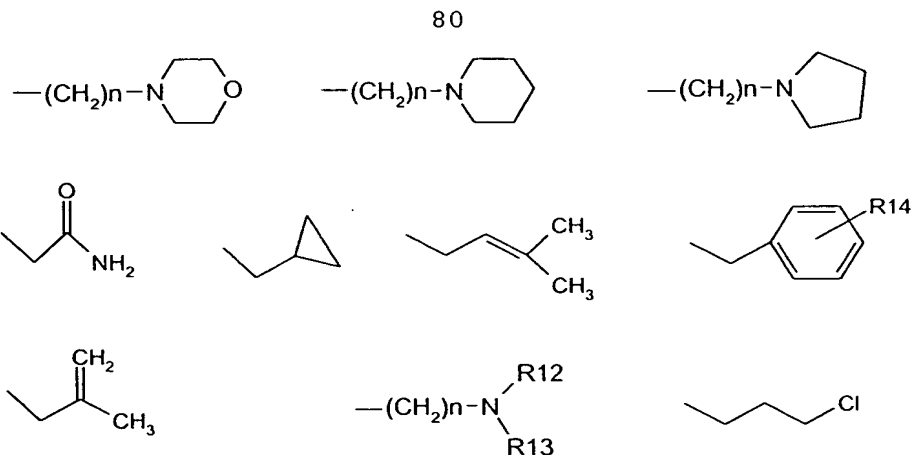


Ib

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wherein Y_3 and Y_4 alternatively mean H and OH, X is Cl, Br or I, Z_2 is oxygen (N-oxide and no counterion), branched or straight chain (C_1-C_6) alkyl, or (C_2-C_7) alkenyl or (C_2-C_7) alkynyl or a group selected from:

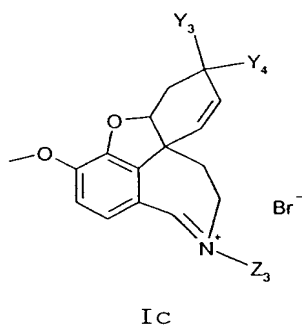
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wherein n , R_{12} , R_{13} and R_{14} have the meanings as defined in accordance with claim 3.

5

5. Use according to claims 1 or 2, characterized by the fact that the used galanthamine derivatives have the general formula Ic



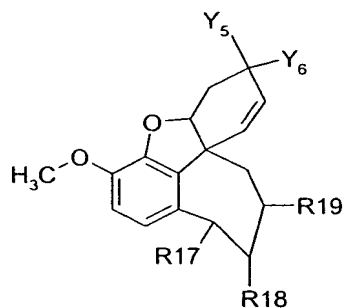
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wherein Y_3 and Y_4 the meaning defined in accordance with claims 3 or 4 have, and Z_3 is oxygen (N-oxide and no counterion) or is a methyl.

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6. Use according to claims 1 or 2, characterized by the fact

that the used galanthamine derivatives have the general formula Id



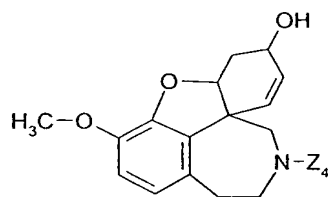
Id

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and their salts, wherein Y_5 and Y_6 alternatively are H or OH, or together form a keto group, and R_{17} , R_{18} , R_{19} are alternatively for two substituents H, wherein the third substituent is NH_2 or $CONH_2$.

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7. Use according to claim 1 or 2, characterized by the fact that the used galanthamine derivatives have the general formula Ie



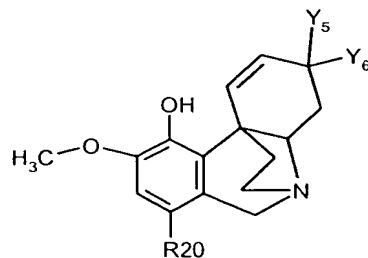
Ie

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or their salts, wherein Z_4 is straight chain or branched (C_1 - C_6) alkyl or 4-brombenzyl.

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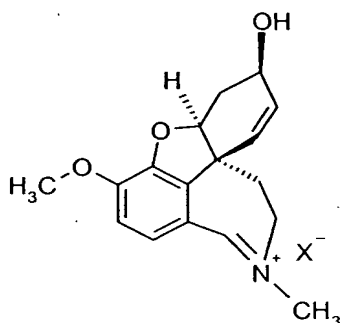
8. Use according to claims 1 or 2, characterized by the fact that the used galanthamine derivatives have the general formula If:



If

or their salts, wherein Y_5 and Y_6 have the meanings as defined in claims 3 to 7, and R_{20} is H or Br.

- 5 9. Use according to claims 1 or 2, characterized by the fact that the used galanthamine derivative has the following structural formula



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- and its pharmaceutical acceptable salts, hydrate or a solvate thereof and having the chemical name (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium.

10. Use according to claim 9, characterized by the fact that the pharmaceutical acceptable salt counterion of (4aS, 6R, 8aS)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a,3,2-ef][2]benzazepinium is selected from the group of halides, preferably bromide, carboxylic acids with 1-3 carboxyl functions, particularly preferably tartrate, malonate, fumarate and succinate, and sulfonic acids, preferably methane sulfonic acid.

Abstract

The invention relates to the use of galanthamine and the cholinergically active derivatives thereof in the production of
5 medicaments for preventive treatment of postoperative delirium and/or subsyndromal postoperative delirium. Galanthamine, the galanthamine derivative(4aS, 6R, 8aS)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10-tetrahydro-6H-benzofuro[3a, 3, 2-ef]
[2]benzazepinium bromide and analogous salts, hydrates or solvates
10 are advantageously suited for use according to the invention.